THE NEURAL REPRESENTATION OF SUBJECTIVE REWARD VALUATION

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Original research articles included in this doctoral thesis

Experiment 1:
Koeneke S., Pedroni A.F., Dieckmann A., Bosch V, Jäncke L. (2008) Individual preferences modulate incentive values: Evidence from functional MRI. Behav Brain Funct 4: 55.

Experiment 2b:
Andreas Pedroni, Susan Koeneke, Agne Velickaite, Lutz Jäncke. (2011) Differential Magnitude Coding of Gains and Omitted Rewards in the Nucleus Accumbens. Brain Res 1411: 76-86.

Experiment 3:
Andreas Pedroni, Nicolas Langer, Michael Allemand, Lutz Jäncke. (2011) Electroencephalographic Topography-Measures of Experienced Utility. J Neurosci 31(29): 10474-80.

1 Abstract

This thesis presents three neuropsychological experiments in the context of subjective valuation of rewards. In all experiments healthy human subjects played a similar wheel-of-fortune game, where they could obtain rewards differing in the subjectively perceived value. Neuronal activity was registered while subjects anticipated rewards and evaluated feedback about outcomes using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG).

In **Experiment 1** the subjective reward value was operationalized as chocolate bars of differently preferred brands. The individual preferences of each subject were correlated with fMRI activity, indicating those areas of the brain sensitively responding to subjective value of rewards.

In **Experiment 2** subjects played a modified wheel-of-fortune game for differently preferred vouchers for a pair of sneakers of a specific brand. Besides investigating fMRI activations throughout the whole brain, temporal runs of hemodynamic responses in the ventral striatum were examined in comparison to well-known single cell spiking patterns in midbrain dopamine neurons of monkeys.

In **Experiment 3,** reward value was modulated, using monetary rewards. In contrast to behaviourally assessed subjective reward value in Experiment 1 and Experiment 2, the subjective reward value of money was estimated by means of electrophysiological measures. In addition, Experiment 3 provided new insights in the temporal dynamics of reward outcome processing taking a data-driven analysis approach.

This thesis therefore explored the neuronal processing of subjective reward value at different scales, ranging from contextual influences such as the influence of brands on valuation to very basal mechanisms of reward coding in the ventral striatum. In addition, using the neuroimaging methods of functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) in a complementary fashion we were able to explore anatomical as well as temporal characteristics of reward value processing.

In dieser Dissertation werden drei Experimente vorgestellt, welche die neuropsychologischen Grundlagen von subjektivem Wert explorieren. Den Experimenten ist gemein, dass die Versuchpersonen ein Glückspiel spielten, bei dem

sie Objekte gewinnen konnten, welche sich im subjektiven Wert unterschieden. Hierbei wurde neuronale Aktivität mittels funktioneller Magnetresonanz Tomographie (fMRT) und Elektroenzephallographie aufgezeichnet, zum einen während der Erwartung auf einen potentiellen Gewinn und nachdem Rückmeldung über den Ausgang des Spiels gegeben wurde.

In **Experiment 1** wurde subjektiver Wert in Form unterschiedlich präferierter Schokolademarken operationalisiert. Die individuelle Präferenz wurde mit fMRT-Aktivität korreliert. So konnte eruiert werden welche Hirnareale subjektiven Wert verarbeiten.

In **Experiment 2** spielten Versuchspersonen eine modifizierte Version des Glückspielparadigmas von Experiment 1. Es konnten unterschiedlich präferierte Gutscheine für Turnschuhe gewonnen werden. Neben fMRT-Ganzkopfanalysen wurden hämodynamische Antwortmuster im ventralen Striatum mit den Resultaten aus früheren Einzelzell-Studien bei Affen verglichen.

In Experiment 3 wurde subjektiver Wert durch Geldwert moduliert. Im unterschied zu verhaltenstechnisch erfassten subjektiven Belohnungswerten in Experiment 1 und Experiment 2 wurde der subjektive Wert von Geld mittels EEG ermittelt. Der neue daten-getriebene Analyse-Ansatz lieferte neue Erkenntnisse über die zeitliche Verarbeitung von Belohnungsreizen.

Zusammengefasst thematisiert diese Dissertationsarbeit die neuronale Verarbeitung von Belohnungswerten auf verschiedenen Ebenen. Diese reichen von kontextuellen Einflüssen von Marken auf die Bewertung von Objekten bis zur Beschreibung sehr basaler Verarbeitungsmechanismen im ventralen Striatum. Die komplementäre Kombination von fMRT und EEG ermöglichte es anatomische und zeitliche Aspekte der Verarbeitung von Belohnungsgrösse zu untersuchen.

2 Summary

As every day experience demonstrates, brands have the power to modulate the subjectively perceived value of objects. **Experiment 1** and **Experiment 2** tested whether it is possible to depict brand-dependent subjective preferences of objectively similar (with respect to monetary value) products by means of fMRI activity in reward-related areas in the human brain. For this purpose, subjects played a virtual wheel-of-fortune game in the MRI-scanner, where they could win differently preferred branded objects (chocolate bars in experiment 1 and sneakers in experiment 2).

Results of both experiments indicated that while anticipating a desired object, hemodynamic responses in the premotor cortex, the anterior insula / later orbitofrontal cortex and the midbrain were scaled with respect to the specific preference. Only in Experiment 2 the ventral striatum revealed brand-preference related increases in neuronal activity. This difference is likely due to modifications in the reward scheme, highlighting the sensitivity of fMRI results with respect to modifications in the experimental taks. In summary, the identified preference-sensitive structures represent a network, which is involved in emotional processing and the initiation of goal-oriented behaviour. This finding also supports the ascribed motivational, action-relevant characteristics of brands.

After subjects were informed about the outcome of the wheel-of-fortune game neuronal activity in the ventral pallidum, caudate nucleus, precuneus, lingual gyrus and in the cerebellum was scaled in dependency of preference. However, these findings were specific to Experiment 1. In Experiment 2 mainly structures in the prefrontal cortex exhibited preference-dependent activity. Again, the incongruity of these results is likely due to differences in the reward schemes.

In summary, we could validate that differences in the preference for an object, solely due to branding are sufficient to evoke differentiable hemodynamic responses in reward related structures of the brain. In addition, dissociation between anticipatory and evaluative aspects of rewards was demonstrated at a neuronal level. Finally,

Experiment 2 served as a replication with slight modifications in the experimental paradigm and reward category. This made it possible to generalize the findings of Experiment 1 to non-food products, but also provided important practical knowledge about the reliability and sensitivity of fMRI with regards to reward studies.

The **second part of Experiment 2** explored the characteristics of the hemodynamic response patterns in the ventral striatum using a different analysis approach. Ventral striatal activity in humans and dopaminergic midbrain activity measured with electrophysiological methods in monkeys are largely congruent with respect to the processing of many aspects of rewards. This led to the hypothesis that ventral striatal activity may be largely influenced by activity in dopaminergic midbrain structures. Since activity in the dopaminergic midbrain is difficult to measure by means of fMRI we compare single cell firing patterns of monkeys of a recent study with similar experimental design to hemodynamic response patterns in the ventral striatum measured in Experiment 2. Comparing single cell spiking patterns with fMRI responses provided new knowledge about the functional relation between midbrain dopamine neurons and the ventral striatum.

Results indicated that hemodynamic responses in the ventral striatum largely followed the predictions of dopaminergic midbrain responses. Contrasting the findings of single cell studies, hemodynamic responses in the ventral striatum upon reward omission gradually decreased in a reward magnitude-dependent fashion. To further explore this unexpected effect we identified the modulatory sources of the graded decrease using a psychophysiological interaction analysis (PPI), which recognized the dorsal raphe nucleus, a cluster in the lateral orbitofrontal cortex and the anterior cingulate cortex as changing their connectivity with the ventral striatum. This indicates, that neuronal activity in the ventral striatum upon reward omission is influenced through serotonergic input of the dorsal raphe nucleus as well as input of the lateral orbitofrontal cortex.

Experiment 3 focussed on the evaluation of rewarding outcomes. To complement on the previous studies a similar experiment as was conducted while registering scalp electroencephalographic signals (EEG). Subjects played a wheel-of-fortune game for different amounts of money ranging from 10 Swiss centimes to 1 Swiss franc in decrements of 10 centimes.

We developed a new analytical method permitting to estimate non-linear monetary reward value functions that can be covaried with event related potential (ERP)

topographies. To our knowledge, these value functions represent the first attempt to identify an electrophysiological correlate of experienced utility, which has been largely neglected in empirical economical research. Finally, the introduced framework of analysis potentially enlarges the scope of ERP studies by accounting for the inherent properties of high-density EEG datasets as well as continuously scaled (non-)linear external variables.

3 Introduction

With the advent of information age, many parallels have been drawn between human brains and computers. To some degree, that may be operationally accurate. But in contrast to a human brain, a computer has no internal goals. We have to tell the computer what to achieve. For humans as for any living organism survival and reproduction constitute the prime goals. To successfully follow these goals we need to obtain and avoid objects in our environment. To make these decisions, the human brain provides mechanisms to encode and evaluate the rewarding values of objects.

Physiological studies and neuroimaging studies in the last decade have shown that there is a common nominator of brain structures evaluating both, primary reinforcers, like food and secondary reinforcers, like money and higher order rewards as novelty, cognitive and social rewards. Consistently, these types of rewards engage activity in a neuronal circuitry commonly referred to as the "reward system". More specifically the neural structures within this network respond sensitively to the value and the probability of occurrence of a reward. This feature of the brain enables to rank different options to form preferences and thus constitutes the basis of choice- or more generally goal-oriented behaviour.

One important question in the field of research on reward processing and decision-making is how reward values and preferences are neurally processed. So far, many studies have investigated the neuronal correlates of reward-value coding using electrophysiological and functional brain imaging techniques. However, only few studies investigated the processing of reward value at a subjective level. This thesis complements on previous work. Specifically, in one part, it investigates the effect of modulating the individually perceived value of objects through branding by conducting two functional magnetic resonance imaging studies (fMRI). In addition, this thesis compares single cell recordings in non-human primates and fMRI responses in humans in order to gain knowledge about the interplay of neuronal core structures in the reward system. In a second part, it presents an electroencephalography (EEG) study. This study provides the basis to render reward value as a function of EEG-activity, providing a psychophysiological measure of

experienced utlity. In the context of this study an analytical framework is presented, which is the first to account for non-linear relationships between external variables and EEG measures incorporating the inherent full spatio-temporal resolution.

4 The neural basis of reward processing

4.1 Neuroanatomy of the reward system

The most important structures involved in the processing of reward information are the ventral tegmental area (VTA), the substantia nigra pars compacta (SNc), the nucleus accumbens (NACC) together with adjacent parts of the caudate nucleus and ventral portions of the putamen forming the ventral striatum (VS). Many areas of the brain interact with these "core" structures, such as the ventromedial prefrontal cortex (VMPFC), the orbitofrontal cortex (OFC) as well as the anterior cingulate cortex (ACC).

The core structures of the reward system are sited along dopaminergic pathways arising in the midbrain. These pathways project via the limbic cortex to the neocortex. Three major pathways can be distinguished (Abler et al., 2005, Roth and Dicke, 2005):

- The **mesotriatal pathway** has its origin in the SNc and the VTA and projects to the dorsolateral hypothalamus and the striatum including the NACC.
- The **mesolimbic pathway** includes projections originating in the VTA and the medial SNc reaching the bulbus olfactorius, the amygdala, the hippocampus and the NACC.
- The **mesocortical pathway** includes neural projections from the VTA and SNc to the prefrontal cortex including the OFC, dorsolateral prefrontal cortex (DLPFC), and the ACC.

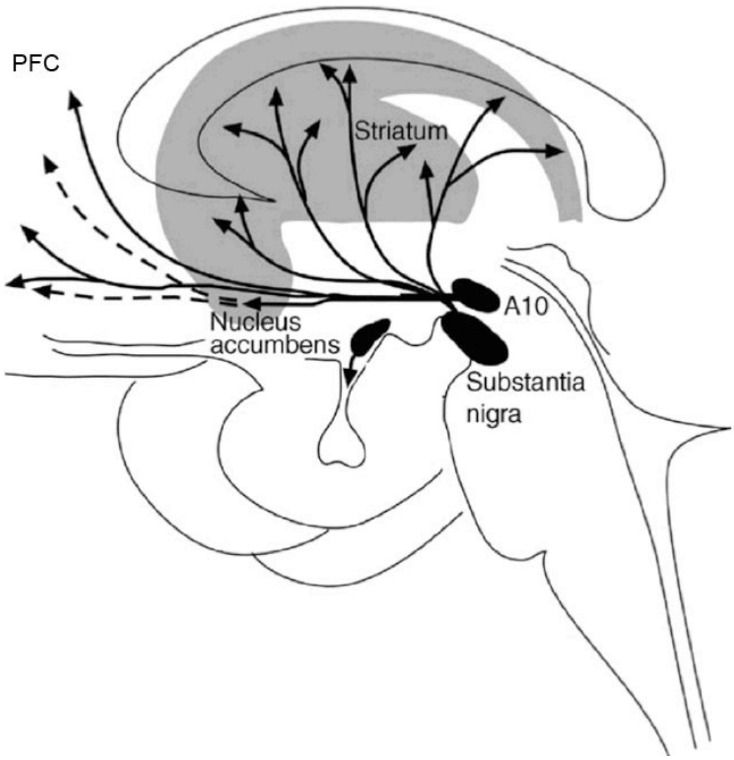

Figure 1: Schematic view of the mesolimbic and mesocortical dopaminergic pathways. (Abler et al., 2005)

Besides this anatomical classification the increasing number of neuroimaging studies in humans and physiological studies in non-human primates suggest a core reward network from a functional point of view; the cortico-basal-ganglia network. It includes the prefrontal cortex, the entire VS, and the dopamine neurons of the midbrain (Haber and Knutson, 2009). The VS receives its main cortical input from the OFC and ACC and massive dopaminergic input from the midbrain. The VS projects to the ventral pallidum (VP) and to the VTA/SN, which in turn project back to the prefrontal cortex, via the medial dorsal nucleus of the thalamus. In addition, other structures including the amygdala, hippocampus, lateral habenular nucleus and specific brainstem structures, such as the dorsal raphe nucleus regulate the reward circuit (Haber and Knutson, 2009).

4.1.1 Prefrontal cortex and anterior cingulate cortex

Neurons throughout the whole prefrontal cortex of primates respond to rewarding stimuli. However, the most important cortical areas to name are the OFC and the ACC. The OFC encompasses Brodmann areas 11, 12, 13, and 14. It is further distinguished between lateral parts of the OFC and medial portions. The ACC covers Brodmann areas 24, 25, and 32 and is subdivided into the dorsal ACC and the subgenual ACC, often also referred to as the ventromedial prefrontal cortex (VMPFC) (Haber and Knutson, 2009).

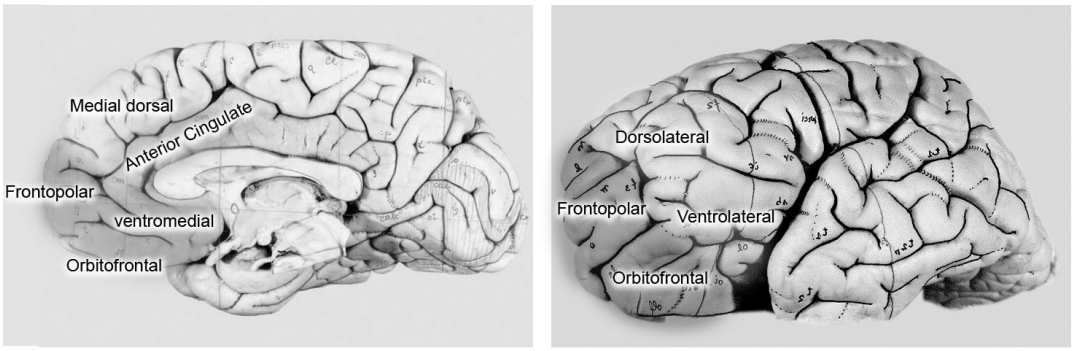

Figure 2. Subdivision of the prefrontal cortex.

Human fMRI and PET studies indicate that various types of rewards recruit activity in the prefrontal cortex. For example it was shown that exposure to primary and secondary rewards consistently increases hemodynamic responses throughout the prefrontal cortex, but convergingly in the VMPFC (Aharon et al., 2001; Blood and Zatorre, 2001; Elliott et al., 2000; JO'Doherty et al., 2001; Knutson, 2000; Small et al., 2001). In addition to the VMPFC, the ACC as well as the dorsal prefrontal cortex seem to be consistently involved in reward processing.

As proposed by human lesion data (Bechara et al., 1994) and several neuroimaging studies activity in the OFC is related to the processing of information about abstract as well as sensory rewards. A recent meta analysis (Kringelbach, 2005) suggests that posterior portions of the OFC tend to respond to sensory rewards (e.g. food), whereas abstract rewards (e.g. money) tend to induce activity in the anterior OFC. In addition, O'Doherty et al. (2001) conjectures that lateral regions of the OFC are recruited, when

events are punishing to inhibit ongoing motor responses, whereas medial parts of the OFC respond to positive events.

The adjacent VMPFC has been implicated in the processing of contextual aspect during the anticipation of rewards. For example, Knutson and Peterson (2005) have shown that VMPFC activity not only correlates with the magnitude of anticipated rewards but also with the probability of occurrence of an anticipated reward. Furthermore, in the context of financial risk taking the weighting of benefits vs. cost is associated with activity in the VMPFC (Knutson and Peterson, 2005; Preuschoff et al., 2006). In summary the VMPFC is conjectured to play a key role in integrating reward value across different stimulus dimensions, possibly through close interplay with the insula and the VS.

The ACC and the dorsal PFC are also involved in reward processing, but activity in these regions is possibly not directly related to valuation. The ACC can be viewed as structure with integrative functions, combining and processing affective, cognitive and motor functions. This integrative aspect of the ACC is in line with the widespread connections to other affective, cognitive and motor areas. With regards to reward processing, the ACC plays a dominant role in the processing of errors. More specifically, the ACC receives input from dopaminergic sites such as the NACC and the VTA and is suggested to integrate reward specific signals to adapt behavioural responses. For example, the consideration of options that conflict on different dimensions, like the price and the preference for an object elicits increased activation in the ACC (Knutson et al., 2007).

4.1.2 Ventral striatum

The ventral striatum, first conceptualized by Heimer (1978) includes the NACC and the broad continuity between the caudate nucleus and the putamen ventral to the rostral internal capsule, the olfactory tubercle, and the rostrolateral portion of the anterior perforated space adjacent to the lateral olfactory tract (Haber and McFarland, 1999). The boundaries between the VS and dorsal striatum are not well defined in terms of cytoarchitectony or histochemistry. Instead, Haber and Knutson (2009) suggest to define the VS as the area within the striatum with afferent projections from reward related structures, namely the VMPFC, OFC, ACC and the medial temporal lobe, including the amygdala.

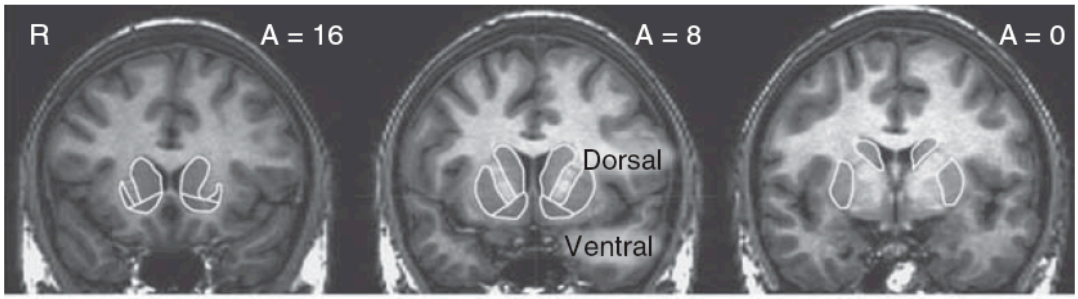

Figure 3. Anatomical distinction between ventral and dorsal striatum. (adapted from Mawlawi et al, 2001)

4.1.2.1 Afferent connections

The whole striatum receives cortical projection organized in a functional topographic manner (Parent et al., 1997). The dorsolateral striatum receives mainly inputs from sensory-motor areas, the central striatum from associative cortices; and the VS is mainly targeted by limbic structures. More specifically, the VS receives a great proportion of glutamatergic input from the cerebral cortex and the thalamus and to a lesser but important proportion, dopaminergic input from the midbrain, primarily from the VTA and SNc (Haber and Knutson, 2009).

4.1.2.2 Efferent connections

The VS primarily projects to the pallidum and the midbrain with the densest terminal fields in the VTA and SN (Parent et al., 1997). In addition, the VS also sends projections to non-basal-ganglia structures, such as the lateral hypothalamus and the periaqueductal grey (Haber et al., 1990). In addition, axons from the medial VS terminate in the amygdala and the nucleus basalis. The nucleus basalis in turn is the main source of cholinergic fibers to the cerebral cortex, suggesting that the VS may directly influence the cortex, without going through the pallidal and thalamic circuit (Haber and Knutson, 2009).

4.1.2.3 Functions of the VS

As outlined above, the VS takes a central role within the network of reward related structures in the brain, integrating emotional/affective information from limbic structures and higher cognitive information to modulate motor functions. In various fMRI and PET studies it has been shown that activation of the VS increases after exposure to primary rewards (e.g. pleasant tastes and sounds) as well as secondary rewards (e.g. monetary rewards) (Blood and Zatorre, 2001; Kunig et al., 2000; Small et al., 2001), indicating that VS activation is independent of the sensory modality of the reward. A line of research has suggested, that VS activity is mainly due to arousal and that not necessarily the most rewarding stimuli elicit increased hemodynamic responses in the VS, but the most salient stimuli (Zink et al., 2006; Zink et al., 2004). However, the omission of an unexpected reward - which is at least as salient as an unexpected delivery of a reward - produces deactivations in the VS (Knutson et al., 2001a). Therefore, it is conceivable that VS activity is not merely reflecting stimulus saliency, but a compound of reward coding and stimulus saliency coding.

Positive and arousing affective experience is linked to VS activity. For example, ligand-based PET studies have implicated, that after amphetamine injection, or consumption of alcohol and cocaine striatal dopamine concentration increases. These increases have been shown to correlate with self-reports of arousal and hedonic experience (Cox et al., 2009; Drevets et al., 2001). Also secondary reinforcers such as playing video games and gambling may also increase dopamine release in the VS (Koepp et al., 1998; Zald et al., 2004).

Besides pure effects of exposure of rewarding stimuli inducing VS activation, a long line of research has conjectured, that many dimensions of rewards, such as reward magnitude, probability, uncertainty, and delay, modulate VS activity. fMRI studies have shown, that VS activity increases proportionally to the magnitude of anticipated rewards (Knutson et al., 2001b; Yacubian et al., 2006). Depth-electrode recordings of epileptic patients in the NACC, indicate a similar effect (Cohen et al., 2009). The probability to obtain a reward relates to uncertainty: High or low probabilities impose small uncertainty, whereas moderate ranges of probability imply maximal uncertainty. With regards to uncertainty and probability there is no consensus on the influence of VS activation. Some studies report linear effects of anticipated reward probability on

VS activity (Abler et al., 2006; Hsu et al., 2009; Tobler et al., 2008; Yacubian et al., 2006) others studies find that the VS is maximally activated with maximal uncertainty (Cooper and Knutson, 2008; Dreher et al., 2006).

Another contextual effect influencing VS activity is the delay between the cue for a reward and the time point where it is obtained. People tend to discount rewards, which are obtained in the far future compared to immediate rewards. fMRI studies have pointed out that VS activity increased when immediate vs. delayed rewards were subjected and decreased with the delay of future rewards (Kable and Glimcher, 2007).

In addition to the above-described effects on VS activity for anticipated rewards, subcomponents within the VS also respond to rewarding outcomes. Results of several studies suggest that hemodynamic responses in the medial caudate portion of the VS are associated with rewarding outcomes (Delgado et al., 2000; Nieuwenhuis et al., 2005) (Kuhnen and Knutson, 2005). Opposing to increased activation of the medial caudate, several studies have reported decreased hemodynamic responses in the VS to the omission of rewards (Berns et al., 2001; Ramnani et al., 2004). Also in the context of reinforcement learning it was shown with computational modelling techniques that the VS tracks the difference between expected and obtained rewards (prediction error) (McClure et al., 2003a; McClure et al., 2003b; O'Doherty et al., 2003). However, VS activity is less consistently observed to reward outcomes as reward anticipation, which is possibly due to the low temporal resolution of fMRI. It is possible that the hemodynamic responses to reward anticipation (a necessary prerequisite for outcomes) wash into the phase of reward outcome and are therefore hardly separable with fMRI.

4.1.3 Midbrain Dopamine Neurons

The midbrain dopamine neurons are classically divided into the substantia nigra pars compacta (SNc), the ventral tegmental area (VTA) and retrorubral cell groups (Haber and Knutson, 2009). The SNc is sited in between the ventral and lateral superior cerebellar peduncle and the red nucleus, forming a band with the VTA.

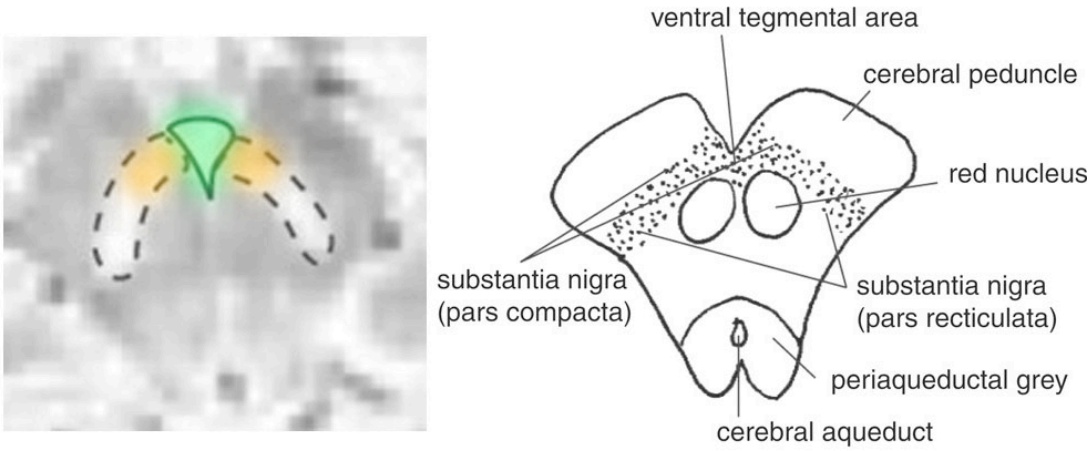

Figure 4. Left panel: Localization of midbrain dopamine nuclei with proton density weighted MRI. The substantia nigra pars compacta (orange) is located in the lateral portions of the midbrain between the cerebral peduncle and the red nuclei. The ventral tegmental area (green) is located in between the substantia nigra pars compacta. (Adapted from D'Ardenne et al., 2008).

4.1.3.1 Afferent projections

Midbrain dopamine neurons receive mainly inputs from the striatum and brainstem regions. In addition, the bed nucleus of the stria terminalis and the sublenticular substantia innominata and the extended amygdala send projections to midbrain dopamine cells. Furthermore, glutamatergic input comes from the pedunculopontine nucleus as well as serotonergic input from the dorsal raphe nucleus (Lavoie and Parent, 1994). Interestingly, dopaminergic midbrain neurons are also connected to the superior colliculus, suggesting a direct sensory input (May et al., 2009). Finally, there is a small proportion of afferents from the PFC, terminating in the VTA and SNc (Haber and Knutson, 2009).

4.1.3.2 Efferent projections

Vice versa to striatal input to dopamine midbrain neurons the main proportion of the output of midbrain dopamine neurons target the striatum (Haber and Knutson, 2009). The projections to the striatum are topographically arranged: Ventral SNc neurons project to the dorsal striatum, whereas the VTA primarily projects to the VS in particular to the NACC.

4.1.3.3 The Functions of midbrain dopamine neurons

Various electrophysiological studies have shown, that the firing rates of midbrain dopamine neurons in monkeys are altered through the prediction of rewards and reward prediction error (Schultz, 2000). Nowadays, improved spatial resolution and newly developed scanning procedures enable to visualize hemodynamic changes in midbrain structures. Although, there are only a limited number of fMRI studies in humans investigating dopaminergic midbrain activity, results suggest that, similarly as in single cell recordings, activity increases during the anticipation of rewards (e.g. pleasant tastes) (D'Ardenne et al., 2008; O'Doherty et al., 2002). Yet, there is no study investigating effects of reward prediction errors in the dopaminergic midbrain in humans.

The before discussed structures of the reward system are by far not the only ones involved in reward processing but are regarded as the key reward structures. Reward processing involves not only the extraction of reward related information of a stimulus. In addition, what counts as a reward and how it is approached has to be learned. Therefore reward processing implies a complex integration between motivational, cognitive-strategic and motor-processes. Thus, depending on the specific task, almost any structure in the human brain may be involved in reward processing.

4.2 The dopamine reward prediction error (DRPE) model

The dopamine reward prediction error model is based on series of seminal studies of the workgroup around Wolfram Schultz. Schultz and colleagues investigated single cell responses in the dopaminergic midbrain of non-human primates in the context of classical and operant conditioning. The first studies indicated, that a large proportion of neurons in the VTA and SNc show phasic increases in firing rates when monkeys are exposed to unexpected primary rewards, like a sip of sweet liquid. These phasic bursts were followed by a postsynaptic release of dopamine (Schultz et al., 1992). Intriguingly, the same neurons exhibited a different response pattern after monkeys have learned that a stimulus cues a forthcoming reward: The phasic response was shifted from the time-point of the reward to the time-point of the cue. In addition,

when a cued reward was unexpectedly omitted, dopaminergic neurons showed a phasic decrease in spiking below the baseline-firing rate. A study of Tobler et al., (2003) showed, that dopaminergic neurons exhibit the same phasic increase in spiking when a cue signalling the omission of a reward is unexpectedly followed by a reward. This supports the hypothesis that dopaminergic neurons encode rewards in relation to the expectancy. It was suggested that such a mechanism is suitable for reinforcement learning. For example, if an action that is expected to result in a rewarding consequence is not followed by a reward, the expectation for the outcome of a subsequent identical action is updated (lowered in this case). Therefore, if one knows about the contingencies between action and outcomes, no further learning has to be made. Whereas, to behave optimally when confronted with a new situation the action-outcome relation has to be first established. Astonishingly, the dopamine reward prediction error (DRPE) model follows the rules of a beforehand-developed computational learning model termed temporal difference (TD) learning by Sutton and Barto (1990). Specifically, it was shown, that the firing rate of dopamine neurons in the VTA and SNc mimic the error function in the TD-algorithm (Schultz et al., 1997).

The firing patterns of dopaminergic midbrain neurons are not an all or nothing response, but are scaled to different variables of reward, like the magnitude, the probability and the uncertainty. As outlined before, neurons in the VTA and SNc increase their firing rate, when a cue predicts a forthcoming reward. Furthermore, the frequency in spiking is correlated to the magnitude / value and expected probability of a reward (Fiorillo et al., 2003; Tobler et al., 2005). It was suggested, that the reward-predicting signal might correspond to the economical construct of expected value (see chapter 3.3.1). In contrast to phasic responses, coding value and probability, tonic increases in dopaminergic spiking seem to encode uncertainty (maximal firing rates at 50% chance for a reward).

Similarly, as neuronal responses to the expectation of a reward, neuronal spiking in response to reward prediction errors (e.g. responses to the exposure of rewards) exhibits very specific patterns. When rewarding cues provide explicit information about putative forthcoming rewards of different magnitudes, firing patterns representing the reward prediction error appear to normalize to the standard deviation of the reward prediction error. For example a single cell monkey study showed, that, when three cues predicted pairs of rewards of different magnitudes with equiprobable

chances of gain, the better outcome always elicited the same positive reward prediction error signal, irrespective of reward magnitude. The same holds for the negative outcomes, which were followed by the same negative reward prediction error signal. As a consequence of this "gain adaptation", the neural responses appear to discriminate between two potential outcomes equally well, regardless of their absolute magnitude differences. Therefore, the dopaminergic system can adapt its sensitivity to a wide range of reward magnitudes (Tobler et al., 2005).

The delineated response characteristics of midbrain dopamine neurons demonstrate, that there is a neuronal signal that breaks down many aspects of reward related information to a common integrated signal. Dopamine neurons, therefore integrate reward related information, extracted and processed in the PFC, VS, ventral pallidum, amygdala, hypothalamus etc. and initiate further processing involved in learning, motivation and executive function.

The work on dopamine neurons in monkeys has also inspired research using EEG in humans. Researchers have identified event related potential (ERP) modulations called the feedback-related negativity (FRN) and the error-related negativity (ERN) that have been suggested to reflect a reward prediction error signal, which shares many characteristics as reward prediction error signals found in midbrain dopamine neurons (Holroyd and Coles, 2002, Cohen et al., 2007, Nieuwenhuis, et al., 2004). It has been proposed that the FRN reflects the effect of midbrain dopamine signals. This conjecture is supported by animal work, demonstrating that midbrain dopamine neurons project to and modulate activity in pyramidal cells in the cingulate cortex (Onn and Wang, 2005). However, the ventromedial prefrontal cortex was also shown to modulate activity of midbrain dopamine neurons (Gao et al., 2007).

In addition to research with EEG, the discovery that the activity of dopamine neurons bears a striking similarity to prediction error terms in computational theories of learning has also influenced the domain of fMRI research on humans. Computational reinforcement-learning models have been used to model reward prediction error related hemodynamic responses on a trial-by-trial basis. Often, such modelled reward prediction error regressors exhibit significant correlations with hemodynamic responses in the striatum and frontal cortex (Braver & Brown, 2003; McClure et al., 2003a; O'Doherty et al., 2003). They are interpreted as reward prediction errors, which have been signaled from midbrain dopamine neurons.

4.3 Neural basis of reward anticipation and outcome evaluation of rewards in humans

Compared to PET, event related fMRI offers a distinction (in the range of seconds) between phases of neuronal processing. Therefore, the majority of neuroimaging studies focussing on reward anticipation and reward outcome processing were conducted with fMRI. In general, a gambling task, such as a roulette game is the most commonly applied experimental paradigm to investigate the neural bases of reward processing, because different variables, such as reward magnitude, and reward probability can be easily varied and it is possible to play for a large amount of repetitions. Breiter et al., (2001) were among the first who investigated hemodynamic response to varying amounts of monetary rewards. Their results suggested strong involvement of the Amygdala and OFC during the anticipation of a reward and the sublenticular extended amygdala (SLEA), the Nucleus accumbens (NACC) and the hypothalamus showing a scaled neural response in correspondence with the value of received monetary gain. In line, Galvan et al., (2005) report OFC activation during the anticipation of monetary rewards, but in combination with increased hemodynamic responses in the NACC and Thalamus. In another study, Knutson et al., (2001b) found that the ventral striatum (incl. NACC) was strongly active during the anticipation of monetary reward, the mesial prefrontal cortex (PFC), the parietal cortex and the posterior cingulum were active following feedback to the participants of having successfully obtained a reward. During reward anticipation, the NACC activity was positively correlated with the magnitude of the monetary reward and the subjects reported positive affect. Further, studies support the idea that the NACC activity represents the value of positive incentives (Ernst et al., 2005; Gottfried et al., 2003; Knutson et al., 2001a). Besides, the NACC and the OFC in few studies it was shown, that the anterior insula and the amygdala is sensitive to the magnitude of rewards (Smith et al., 2009).

Different structures, than in the anticipation of a reward have been found to be responsive to the magnitude of rewarding outcomes. Many studies consistently identified the VMPFC and the ACC among others, like the OFC and premotor areas (Breiter et al., 2001; Knutson et al., 2001b; Knutson et al., 2003; Rolls et al., 2008).

The VMPFC is thought to modify outcome-related appetitive impulses in goal-directed behavior (Knutson et al., 2003). In the context of reward processing many

studies have shown, that the ACC is activated, when outcomes are worse than expected, which is in line with its ascribed role in conflict monitoring. The OFC on the other hand, harbors representation of reinforcement values (Rolls, 2004). Furthermore, fMRI studies have revealed correlation between OFC activation and ratings of subjective pleasantness (Kringelbach et al. 2003)

4.3.1 Subjective reward value

Economic theories on valuation are directly connected to decision theory. The origin of decision theory is traced to a correspondence between Pascal and Fermant in 1654. They stated, that a decision maker would always choose the option offering the highest expected value (EV).

$$EV = px$$

where p represents the probability of obtaining an outcome of x (e.g. $)

The EV is simply computed by multiplying the probability of a prospect with its' value. According to this theory a subject always would choose 100 Swiss francs with a chance of 50% compared to 49 Swiss francs for sure. Obviously, not everybody would make this choice. Decision makers, who are "risk averse" would rather chose 49 Swiss francs for sure. Swiss mathematician Bernoulli (1738) suggested a solution for this problem. He asserted, that people do not evaluate options by the objective value, but rather by their utility or subjective value. For example, for a poor person, 1000 Swiss francs are more worth, than for a wealthy person. Therefore marginal utility decreases as wealth increases. The linear value function of the EV-theory is exchanged by a concave utility function.

$$EU = pu(x)$$

u(x), represents the utility of obtaining outcome x with the probability of p

Also, the expected utility theory (EUT) received criticism with respect to its validity. It could be experimentally shown, that people do not weight probabilities linearly, but

exhibit risk seeking for low probabilities (overestimating low probabilities) and risk aversion (underestimating high probabilities). These deviations from the EUT led to a new theory, the prospect theory by Kahneman and Tversky, (1979), accounting for the above-described anomalies. The prospect theory makes assumptions on how consequences and probabilities are transformed into subjective values. Similarly as the expected utility theory, overall utility results of an integration of value and probability. However, the utility function in the EUT over states of wealth is replaced by a value function over gains and losses relative to a reference point. Additionally, the value of an outcome is weighted by a decision-weight, representing the impact of the relevant probability on the valuation of the prospect. Therefore, Kahneman and Tverskys' theory relies on the Weber – Fechner law, where psychological response is a concave function of the magnitude of physical change in sensory and perceptual dimension.

$$V(x,p) = v(x)w(p)$$

v represents the subjective value for a consequence x. w weights the influence of the objective probability (p) on the attractiveness of a consequence.

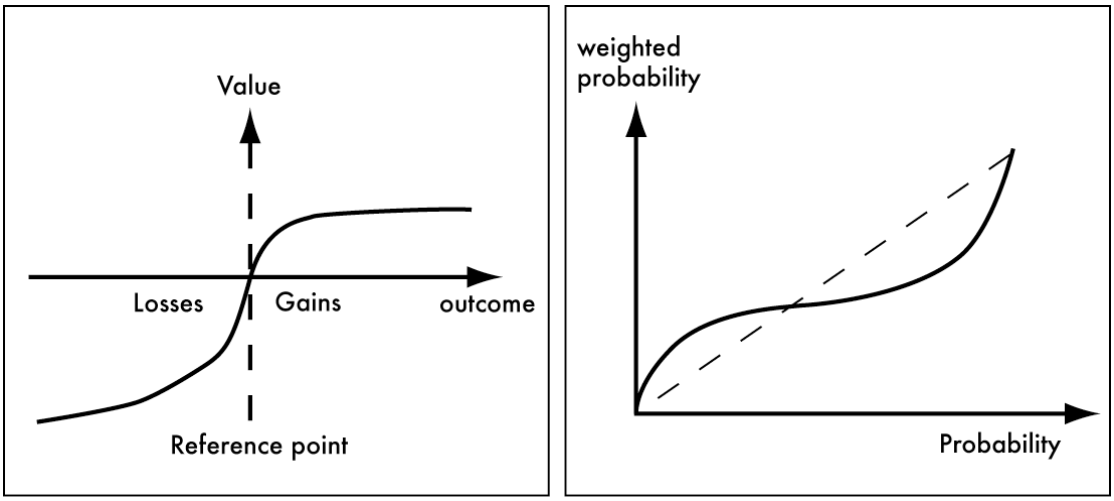

Figure 5. Fictive value function in prospect theory with the corresponding probability weighting function in the right panel.

The major difference to the EVT and EUT is, that the prospect theory takes into account psychological factors (e.g. cognitive biases, motivational and emotional

factors) influencing valuation and the estimation of probabilities. In the following section some major factors influencing the valuation of utility are discussed.

4.3.2 Contextual influences on valuation

As outlined before decision-making is influenced by many psychological factors. For example, people exhibit discounting of valuation for delayed rewards. In humans and non-human primates, this effect was shown on a neuronal level (Freeman et al., 2009; Tesch and Sanfey, 2008; Woolverton et al., 2007). When subjects are faced with rewards in the future compared to instant rewards, activity in the VS was reduced, paralleling the diminishing value of future rewards (Gregorios-Pippas et al., 2009).

Another prime example of contextual influence on reward valuation is that people compare their choices with the outcome of alternative choices. This effect has been shown to influence the valuations of rewards. Several studies have investigated this effect on a neural level (Camille et al., 2004; Coricelli et al., 2005; Coricelli et al., 2007) and suggested that the OFC and amygdala modulate the course of decision-making through strong involvement of emotional inputs. More generally many human neuroimaging studies conjecture that the human reward system largely encodes reward values in relation to possible outcomes and not at an absolute scale (De Martino et al., 2006; Elliott et al., 2008; Fujiwara et al., 2009).

Furthermore, human valuation is strongly influenced by the way information about a prospect is presented. For example, de Araujo et al., (2005) exposed subjects in an fMRI scanner to the odour of isovaleric acid (which has a cheese-like odour), and accompanied it with the words ‘cheddar cheese’ or ‘body odour’. Results indicated that subjects greatly preferred the scent when labelled ‘cheddar cheese’. Additionally they could show that activity in medial orbitofrontal cortex and rostral anterior cingulate cortex coded this subjective experience.

A more ecological valid setting for modulating prospects is given with regards to brands, implying different degrees of preference. McClure et al., (2004), for instance, have shown that participants show stronger hemodynamic responses in reward-related brain regions (dorsolateral prefrontal cortex (DLPFC), hippocampus, midbrain) when receiving a small amount of a soft drink pre-cued by a picture of a Coca-Cola can rather than by a circle of light or a picture of a Pepsi can. Schaefer and Rotte, (2007)

reported stronger activity in the ventromedial prefrontal cortex (VMPFC) and precuneus when participants were presented with logos of luxury and sports car brands compared with pragmatic, more economic car brands. In a study by Deppe et al., (2005), participants were asked to imagine choosing between pairs of brands. The authors reported reduced neural activity in regions associated with working memory and reasoning, and increased neural activity in regions related to emotion processing when presenting the most popular brand in terms of the market share as compared with less popular brands. Based on their findings, the authors postulate a winner-take-all effect of a person's favourite brand on neural activation, an effect that would partially contradict the graded response to different amounts of monetary rewards.

4.4 Research questions

The present thesis sought to investigate the effects of brand preferences on the valuation of rewards within a well-specified psychological framework. In the first part of the thesis, two experiments were conducted in close collaboration with the Basic Research of the Gesellschaft für Konsumforschung, E.V. (GFK), Nürnberg. One goal of the first two experiments was to test the potential of fMRI for consumer research. We therefore critically examined whether fMRI possesses the degree of resolution necessary to detect even relatively small differences between brands that are attractive to varying degrees, but whose ratings are uniformly positive. The other goal of the first two experiments was to explore, which specific structures within the human reward system exhibit brand-preference-modulated activation. Resolving this question should contribute to a better understanding on how brands and cultural information in general influence preferences in humans. At last, the first two experiments were designed to allow for investigating the suggested dissociation between an anticipatory reward component (reward prediction) and an evaluative reward component (reward outcome). This dissociation is important for understanding buying behaviour, since anticipation and evaluation may be associated with different facets of a brand: (a) motivational, action-relevant characteristics, and (b) emotional or cognitive evaluative aspects.

The second part of the thesis focused on more basal aspects of reward valuation. The second experiment was designed to allow for comparing fMRI activity with a previous study of Tobler et al. (2005) examining single cell recordings in midbrain

dopamine neurons of macaques. Additional analyses on the dataset of the second experiment were conducted to explore hemodynamic time-courses in the VS. It was questioned, whether fMRI signals in the VS parallel specific response patterns in monkeys' midbrain dopamine neurons. Secondly, we sought to investigate whether the effect of reward value "gain-adaptation" (see also chapter 3.2), reported in Tobler et al.'s (2005) single cell study is also evident at the level of the VS in humans.

With respect to the slow temporal of fMRI, EEG has the advantage, to resolve correlates of brain activity on a millisecond-scale. In amend on the knowledge gained with fMRI methods we conducted an additional experiment, which was similar to the first two fMRI experiments but recorded correlates of brain activity with EEG. We were therefore interested in the temporal dynamics of reward evaluation. In most EEG studies ERPs at single electrodes within a specific time-window are examined. This common practice reflects a poor statistical and neurophysiologic representation of the high spatial and temporal sampling of modern EEG measurements. In the presented study a new data driven analysis approach was applied incorporating the full spatiotemporal resolution of EEG. The specific aim of the study was to determine at which time-windows ERP topographies covary significantly with reward values of gained and omitted monetary rewards.

5 Experiments

5.1 Experiment 1: Individual preferences modulate incentive values: Evidence from functional MRI

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5.1.1 Abstract

Background

In most studies on human reward processing reward intensity has been manipulated on an objective scale (e.g., varying monetary value). Everyday experience, however, teaches us that objectively equivalent rewards may differ substantially in their subjective incentive values. One factor influencing incentive values in humans is branding. The current study explores the hypothesis that individual brand preferences modulate activity in reward areas similarly to objectively measurable differences in reward intensity.

Methods

A wheel-of-fortune game comprising an anticipation phase and a subsequent outcome evaluation phase was implemented. Inside a 3 Tesla MRI scanner, 19 participants played for chocolate bars of three different brands that differed in subjective attractiveness.

Results

Parametrical analysis of the obtained fMRI data demonstrated that the level of activity in anatomically distinct neural networks was linearly associated with the subjective preference hierarchy of the brands played for. Preference-dependent neural activity has been registered in premotor areas, insular cortex, orbitofrontal cortex, and in the

midbrain during the anticipation phases and in the caudate nucleus, precuneus, lingual gyrus, cerebellum, and in the pallidum during the outcome phases.

Conclusion

Our results suggest a graded effect of differently preferred brands onto the incentive value of objectively equivalent rewards. Regarding the anticipation phase, the results reflect an intensified state of wanting that facilitates action preparation when the participants play for their favourite brand. This mechanism may underlie approach behaviour in real-life choice situations.

5.1.2 Background

What counts as reward differs substantially depending on individual preferences. Branding can elicit robust differences in preferences for consumer products despite their highly similar appearance and may therefore provide an ideal measure of truly subjective preference in that it is largely independent of objective stimulus characteristics. Indeed, branding is often viewed as the addition of value and meaning to often quite mundane and interchangeable products [e.g., 1]. Current theories of reward processing have paid increasing attention to such cultural influences on choice behaviour. Our aim is to expand these theories by examining the modulatory impact of subjective brand preferences on neural activity. Furthermore, the external validity of our findings is greatly enhanced by the high relevance of brands in everyday life.
Most previous research on the neural representation of reward has focused on the manipulation of reward according to an objectively quantifiable scale without therefore having to consider individual differences in preferences. There is no doubt that people have a general preference for larger rather than smaller amounts of money. Many human imaging studies have made explicit use of various degrees of monetary incentive value as means to manipulating reward intensity, and have reported several neural regions that adapt their activity according to change in reward intensity. O'Doherty et al., for example, reported stronger recruitment of the medial orbitofrontal cortex (OFC) upon gaining higher compared with smaller amounts of money in a two-alternative choice task [2]. In another study, Breiter et al. identified the sublenticular extended amygdale (SLEA), the Nucleus accumbens (NACC) and

the hypothalamus as showing a scaled neural response in correspondence with the value of received monetary gain [3]. In addition, neural activation patterns in the SLEA and in the OFC reflected the value of the potential rewards in the period in which participants anticipated the outcome. A later study by Knutson et al. found a dissociation of neural circuits involved in different aspects of reward: While the ventral striatum (incl. NACC) was strongly active during the anticipation of monetary reward, the mesial prefrontal cortex (PFC), the parietal cortex and the posterior cingulum were active following feedback to the participants of having successfully obtained reward [4]. During reward anticipation, the NACC activity was positively correlated with the magnitude of the monetary reward.

However, even the rewarding value of money may be influenced by context effects. Counterfactual reasoning, for example, refers to the human tendency to compare their choices with the outcome of alternatives. Winning Sfr. 5 in gambling most certainly evokes a degree of satisfaction, whereas winning Sfr. 5 while knowing that one could have won Sfr. 10 had one chosen differently evokes regret or disappointment [5]. The neural underpinnings of this effect have recently been investigated [6-8]. The concept of delayed discounting, concerning the point in time when a reward is delivered, is a further example of the effect of contextual information on the perceived value of a certain reward [9, 10, 11, 12]. Early animal studies strengthen this finding [13]. Counterfactual reasoning and delayed discounting, however, reflect population-specific effects, meaning that the contextual information has a similar impact on each subject.

Food, on the other hand, might be a universal primary reinforcer but people greatly differ in their taste preferences. Similarly, interindividual variance in the attractiveness of a reward also characterizes branded consumer goods. The neural representation of brand preferences has recently received considerable attention. McClure, for instance, reported that participants show stronger hemodynamic responses in reward-related brain regions (dorsolateral prefrontal cortex (DLPFC), hippocampus, midbrain) when receiving a small amount of a soft drink pre-cued by a picture of a Coca-Cola rather than by a circle of light or a picture of a Pepsi can [14]. Schaefer and Rotte reported stronger activity in the ventromedial prefrontal cortex (VMPFC) and precuneus when participants were presented with logos of luxury and sports car brands compared with pragmatic, more economic car brands [15]. In a study by Deppe et al., participants were asked to imagine choosing between pairs of

brands [16]. The authors reported reduced neural activity in regions associated with working memory and reasoning and increased neural activity in regions related to emotion processing when presenting the most popular brand in terms of the market share as compared with less popular brands. Based on their findings, the authors postulate a winner-take-all effect of a person's favourite brand on neural activation, an effect that would however partially contradict the graded response to different amounts of monetary rewards.

To our knowledge, however, none of the available studies on brand preferences used participants' stated preferences as a means to specifically varying the subjective attractiveness of the selected brands. Furthermore, previous brain imaging studies of brand preferences did not clearly differentiate between the period of anticipating and that of receiving reward. While this distinction between anticipatory (wanting) and evaluative (liking) components has already been proposed by Berridge on the basis of animal studies [17], and evidence from human studies using monetary reward supports this concept [3, 18], the available studies on brand preferences may have confounded motivational with evaluative components of reward processing. Finally, the use of more than two preference categories is a necessary precondition to unequivocally determining any modulatory influence of brand preference on neural activity pattern. It may well be that, similar to monetary rewards; brand-associated neural activity increases monotonically with the strength of the individual preference for a particular brand.

To address these issues, we developed a wheel-of-fortune game that allowed for the differentiation between an anticipation period (spinning of the wheel; wishing for a positive outcome) and an outcome period (processing the game outcome). Chocolate bars of three different brands could be won. By using chocolate bars as rewarding stimuli we introduced a product category with relatively homogeneous pricing so as to avoid the coupling of reward intensity with monetary value, which may be neurally processed in a different way. Established market research instruments were used prior to the fMRI experiment to determine participants' individual brand preferences. Based on the results of these instruments, brands that differed in subjective attractiveness were selected individually for each participant and used as stimuli in an fMRI experiment. During the experiment, brands were represented by their logos. However, real chocolate bars were given to the participants after the experiment.

The primary aim of our study was to explore whether there are neural structures that modulate their activation according to the subjective preferences for the chocolate bar brands that the participants played for (e.g., higher activity in case of more preferred compared to less preferred chocolate brands). Additionally, the design allowed for investigating the suggested dissociation between an anticipatory reward component (game outcome unknown, wanting) and an evaluative reward component (evaluation of game outcome, liking). This dissociation is important for understanding buying behaviour, since anticipation and evaluation are associated with different facets of a brand: (a) motivational, action-relevant characteristics, and (b) emotional or cognitive evaluative aspects.

5.1.3 Methods

Participants

Nineteen healthy female adult voluntary participants (mean age of 24.05 ± 2.63) were recruited from the University of Zurich and ETH Zurich, Switzerland. Participants were selected based on a two-stage selection procedure. At the first stage, a paper and pencil questionnaire was distributed to students in different courses of the Psychology Department of the University of Zurich. Ninety-eight students completed the questionnaire. Of those, thirty-one respondents who indicated that they (a) ate chocolate at least from time to time, (b) cared about chocolate, (c) cared about brands when it came to chocolate and who expressed differentiated brand preferences in a constant sum point allocation "chip game" between different chocolate brands, were invited to the second round. Given that the majority of the participants who passed this first phase were female, we decided to restrict the study to women. However, we do not expect gender differences in the neural representation of rewards differing in subjective attractiveness. Twenty-seven of the pre-selected participants accepted the invitation and filled out a second, computer-based questionnaire that aimed at measuring individual brand preferences in more detail with a choice-based procedure (the GfK Price Challenger, GPC) and, again, with a constant sum chip game. Of those, twenty respondents who expressed preferences that were consistent across the two measures and widely dispersed to allow for clear brand differentiation were finally invited to the fMRI study. One participant dropped out for private reasons. The

remaining nineteen participants gave informed consent approved by the local ethics committee. Participation was compensated with 50.00 sFr and the amount of chocolate bars won.

Task design

Participants played a virtual wheel-of-fortune game presented via a video projector onto a translucent screen that participants viewed inside the scanner via a mirror. The experiment consisted of four runs with 30 trials each. Routinely, individual T1-weighted anatomic brain images were recorded before the actual experimental sessions started. The total scanning time was approximately 50 minutes.

Before being scanned, participants were carefully informed with respect to the MRI / fMRI method. Following this, each participant had to (1) complete a questionnaire that checked for individual MR-suitability and (2) to give his / her written informed consent. Then, participants were requested to read a short instruction manual, which explained the procedures of the experiment, and played two trials of the wheel-of-fortune game outside the scanner in order to make sure that they had understood the task.

The experiment had a 3 x 2 x 2 factorial design: Participants played for three different chocolate brands (1st factor). These brands were selected based on the preference data gathered in the second stage of the selection procedure. For each participant, her favourite and her least preferred yet still acceptable brand were selected, as well as one intermediate brand that ranked between the top and the bottom brand. There were two types of trials (2nd factor), winning trials and losing trials, with two possible outcomes, respectively (3rd factor): In winning trials participants either won or did not win a chocolate bar; in losing trials, already won chocolate bars were either lost or not lost. The main focus of our study was on the hemodynamic responses to winning trials, that is, to positive anticipation and outcomes. We implemented separate losing trials rather than combining winning and loosing in one trial (win a chocolate bar vs. loose a chocolate bar) in order to detach negative, apprehensive processes that might predominate in some participants from more cheerful positive expectancy. There is recent empirical evidence that participants anticipate emotional events of unknown valence to be negative or unpleasant [19]. By separating the anticipation of positive from the anticipation of negative outcomes we circumvented this potential problem.

Participants were randomly assigned to one of six different pseudorandom trial sequences. In each trial, the chance of winning or losing a chocolate bar was approximately fifty percent. Also the brands the participants played for were pseudo-randomly distributed to ensure enough trials of every possible combination (brand x trial type x outcome) for the analysis.

One trial consisted of an announcement phase (1 sec.), a response phase (0.2 - 2 sec), an anticipation phase (10 sec.), an outcome phase (3 sec.), and a blank screen with a fixation cross (6 sec.; see Figure 1). In the announcement phase the brand logo was presented in the middle of a wheel of fortune with six colored (green for wining trials, red for losing trials) and six black fields. The colors indicated the trial type (winning trial vs. losing trial). During the response phase, participants could control the entry speed of the rotation of the wheel of fortune by pressing a button early or late within the time window. This was implemented to give participants the feeling of being actively involved in the game Additionally, the variable response latency (200 ms – 2000 ms) induced a dephasing of stimulus onsets with respect to scan onsets to optimize sampling of the hemodynamic response. The entry speed did not affect the (pseudo-randomized) outcome of the prior anticipation phase. The anticipation phase started with the wheel of fortune rotating at the selected entry speed, slowing down to halt after 10 seconds. The ensuing outcome-phase started after the wheel had stopped. The outcome was indicated by the field that came to a halt under a pin at the top of the wheel and it was also indicated in a text box (i.e., “You have won/lost 1/0 chocolate bars”). To ensure that the fMRI signal could level back to a task-unspecific baseline, a blank screen with a fixation cross was presented for six seconds before the next trial started.

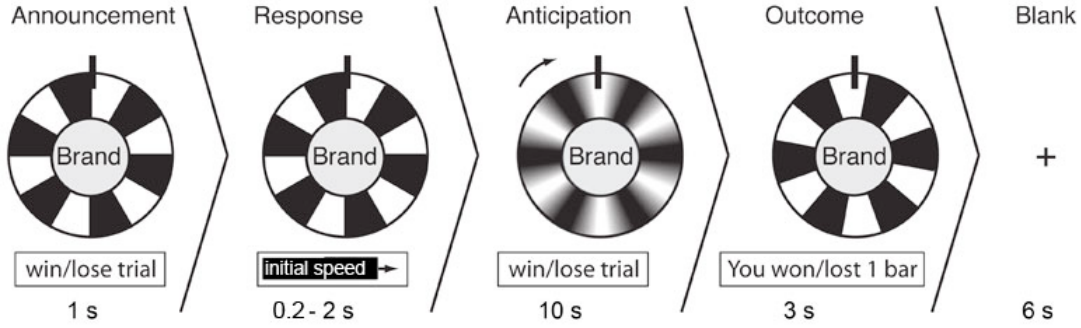

Figure 1. Experimental design of the wheel-of-fortune game

At the beginning of the experiment, each participant started with an account of three chocolate bars of each brand. It had been made clear to participants during the instructions prior to scanning that all major tastes of the brands they played for were available to choose from (e.g., dark chocolate, milk chocolate, hazelnut). Thus, participants did not have to fear that they would end up with tastes they did not like. After each of the four runs the number of chocolate bars was accounted and the balance was visually presented. This balance was transferred to the next run. After the experiment, participants received the total number of chocolate bars won (on average 8.83 chocolate bars), thus ensuring that the wheel-of-fortune game offered real incentives. Finally, after the four runs were finished, the participants were paid 50.00 sFr, given the won chocolate bars in the taste variants of their choice, and dismissed.
Trials in which participants missed starting the wheel of fortune (i.e., did not press the button within two seconds) were regarded as no-interest trials and excluded from the statistical analyses. The total number of missed trials across all participants was 8, with a maximum of two lost trials for two of the participants.

Functional imaging

A Philips Intera 3T whole-body MR unit (Philips Medical Systems, Best, The Netherlands) equipped with an eight-channel Philips SENSE head coil was used to acquire magnetic resonance images at the University Hospital Zurich. Anatomical images of the whole brain were obtained by using a T1-weighted three-dimensional, spoiled, gradient echo pulse sequence (repetition time (TR)=20 ms, echo time (TE)=2.30 ms, flip angle 20°, field of view (FOV)=220 mm, acquisition matrix=224 x 224, voxel size=1 mm x 1 mm 0.75 mm, 180 slices, slice thickness=0.75 mm). Functional data for the behavioural tasks were obtained from 280 whole-head scans per run (1120 for 4 runs) using a Sensitivity Encoded (SENSE) [20] single-shot echoplanar imaging technique (TR = 2500ms, TE = 35ms, flip angle = 78°, FOV = 220mm, acquisition matrix= 80 x 80, 33 transverse slices, voxel size= 1.72 mm x 1.72 mm x 4 mm).

Data analysis

Artefact minimization and MRI data analysis were performed using MATLAB 2006b (Mathworks Inc., Natick, Massachusetts, USA), and the SPM5 software package

(Institute of Neurology, London, UK). The first three images were discarded to allow for steady-state magnetization. All images were realigned to the first image of the first run, spatially normalized into standard stereotactic MNI-space (EPI template provided by the Montreal Neurological Institute), interpolated to a voxel size of 2 x 2 x 2 mm and spatially smoothed using a 8-mm full-with-at-half-maximum Gaussian kernel.

Activated voxels were identified by the "General Linear Model" approach, implemented in SPM5. At the first level of analysis, we adopted a parametric analysis according to Büchel et al. [21]. After highpass-filtering (cut-off 128 s), an individual statistical model was computed for each participant with separate regressors for the response phase (modelled as events), for the anticipation phase of winning and losing trials (each modelled as epochs of 10s), and for each possible outcome type (won winning trial, not-won winning trial, lost losing trial, not-lost losing trial, modelled as epochs of 3s). All regressors were convolved with SPM's canonical difference of gammas hemodynamic response function. The maximal cross-correlation between regressors was on average r = 0.156 (0.033 SD) across all subjects.

Given that the main purpose of the analysis was to identify regions whose hemodynamic response monotonically increased or decreased with individual brand ranking, the ranks of the brands in the individual preference hierarchy were included in the model as modulatory parameters (i.e., 3, 2, 1, from the most to the least preferred brand). Linear contrasts of the first order terms against a baseline (6 seconds rest epoch, blank screen with fixation cross) were performed. This was applied to the anticipation phases of winning trials and losing trials, the outcome phases of winning trials that were won and not won, and the outcome phases of losing trials that were not lost and lost (contrasts are indicated by **1, e.g., WA1). To additionally obtain results of the main effect of the task, individual baseline contrasts were performed using the zeroth order regressor of the respective conditions (contrasts are indicated by **0, e.g., WA0). A complete list of all experimental conditions is given in table 1.

Table 1. List of experimental conditions.

Trial type:	Phase:	Outcome:	Abbreviation:
Winning	Anticipation	Won & not won	WA
Winning	Outcome	Won	WOW
Winning	Outcome	Not won	WOnW
Losing	Anticipation	Lost & not lost	LA
Losing	Outcome	Lost	LOL
Losing	Outcome	Not lost	LOnL

To permit population-level inferences, maps of contrast coefficients for each of the first level contrasts were collectively submitted to one-sample t tests against the null hypothesis of no activation, while controlling for random effects. Given that the outcome phase immediately followed the anticipation phase yields the possibility that clusters of activation found in the outcome phase are also due to continuing activity elicited during the anticipation phase. Taking this possible confound into account, we additionally reduced the search area for activations in the outcome phase (WOW1, WOnW1, LOL1 LOnL1) to the areas activated by the preceding anticipation phase (WA1, LA1). No clusters of activation remained.

To explore the full range of effects in the data, voxels surviving significance thresholding at $p < .001$, uncorrected for multiple comparisons with a spatial extent threshold at $k = 10$ voxel were reported. For specific regions a priori hypotheses could be derived from findings of prior studies using reward paradigms [18, 22, 23, 24]. Small volume corrections (SVCs) were used for these regions to correct the false positive error probability for the number of comparisons made within each region. SVCs were applied with a sphere of 8 mm, chosen to be equal to the spatial smoothing kernel [25, 26, 27]. Peaks surviving $p < .05$ family wise error (FWE) correction were considered significant. The cluster locations were indicated by the coordinates of the voxel at the local cluster maximum and labelled using the automated anatomical labelling (AAL) toolbox [28]. Cluster locations that were not identified with the AAL toolbox were manually labelled with reference to the Harvard-Oxford subcortical structural atlas. By overlaying the statistical parametric

maps on an averaged and normalized structural (T1) image of all subjects, we assured that the reported cluster locations were within the reported neuronal structures.

5.1.4 Results

The main focus of our study was placed on brain regions in which neuronal responses increase or decrease monotonically with increasing brand preference during the anticipation phase preceding winning trials (WA) and the outcome phase following gains in winning trials (WOW). This represents the first order term in the parametric analysis. We also included losing trials into our experiment to balance the amount of gained rewards and to dissociate gain from loss phases (see methods section). For descriptive purposes, we additionally conducted first order parametrical analyses of anticipation phases of losing trials (LA1) and outcome phases of lost losing trials (LOL1) [Additional file 1]. No significant preference modulated clusters ($p < .001$ for multiple comparisons) were located for outcomes with no effect on gaining or losing chocolate bars (WOnW1 and LOnL1) conditions. Thus, the reported findings refer to expectations and outcomes of rewards (chocolate bars) rather than to an unspecific effect of brand logo presentation.

Main effects of task

The effects of the zeroth order term of the parametric analysis (main effect of the tasks) were not of interest for the current study question. For the sake of completeness the corresponding results of WA0 and WOW0 are listed in the supplement.

Regions responding in correlation with preferences during the anticipation phase of winning trials

In the contrasts of the first order parametric modulation of the anticipation phase of winning trials (WA1), several brain areas revealed hemodynamic responses linearly increasing with higher subjective preference: Left caudal premotor area, right rostral premotor area, right lateral orbitofrontal cortex reaching into the anterior insula, right posterior superior temporal sulcus / anterolateral intraparietal sulcus, and the dopaminergic midbrain.

Clusters of voxels showing a linear decrease in neural activity with higher subjective preferences (WA1) were located in the left middle frontal gyrus, left middle cingulate cortex, bilateral precuneus, left calcarine sulcus, left angular gyrus, left lingual gyrus, left fusiform gyrus and right middle cerebellum (Figure 2, Table 2).

Table 2. Clusters with preference-dependent activity during the anticipation phase. All clusters show a probability of error of $p < .001$ uncorrected for whole brain multiple comparisons. The coordinates and t values are at the peak voxels in each cluster (coordinates refer to MNI-space). Clusters written in bold letters are within a priori hypothesized regions and are below a significance threshold of $p < .05$ family wise error corrected for small volumes (sphere with 8 mm radius).

Neural activity in regions	Right/ Left	Cluster Size (Voxels)	Coordinates			t-value
			X	Y	Z	
increasing linearly with subjective preference:						
Caudal premotor area	**L**	**99**	**-16**	**-8**	**62**	**5.89**
Rostral premotor area	**R**	**13**	**16**	**4**	**68**	**3.86**
Lateral orbitofrontal cortex / anterior insula	**R**	**15**	**44**	**28**	**-12**	**3.97**
Posterior superior temporal sulcus/ anterolateral intraparietal sulcus	R	11	42	-48	14	4.18
Dopaminergic midbrain (substantia nigra)	**R**	**33**	**10**	**-18**	**-6**	**4.01**
decreasing linearly with subjective preference:						
Middle frontal gyrus	L	71	-36	12	60	6.02
Posterior cingulate cortex	L	32	-4	-30	40	4.85
Posterior cingulate cortex	L	38	-16	-50	36	4.36
Precuneus	L	443	-4	-50	8	5.67
Precuneus	R		6	-52	14	5.23
Precuneus	L		-2	-58	26	3.84
Precuneus	L	173	-2	-72	34	4.66
Calcarine sulcus	L		-4	-70	16	4.08
Middle occipital cortex	L	88	-42	-76	34	4.74
Angular gyrus	L		-52	-74	26	4.78
Lingual gyrus	L	35	-8	-80	-8	4.34
Lingual gyrus	L		-16	-82	-6	3.92
Fusiform gyrus	L	13	-26	-42	-14	4.28
Middle cerebellum 10	R	15	28	-36	-40	4.65

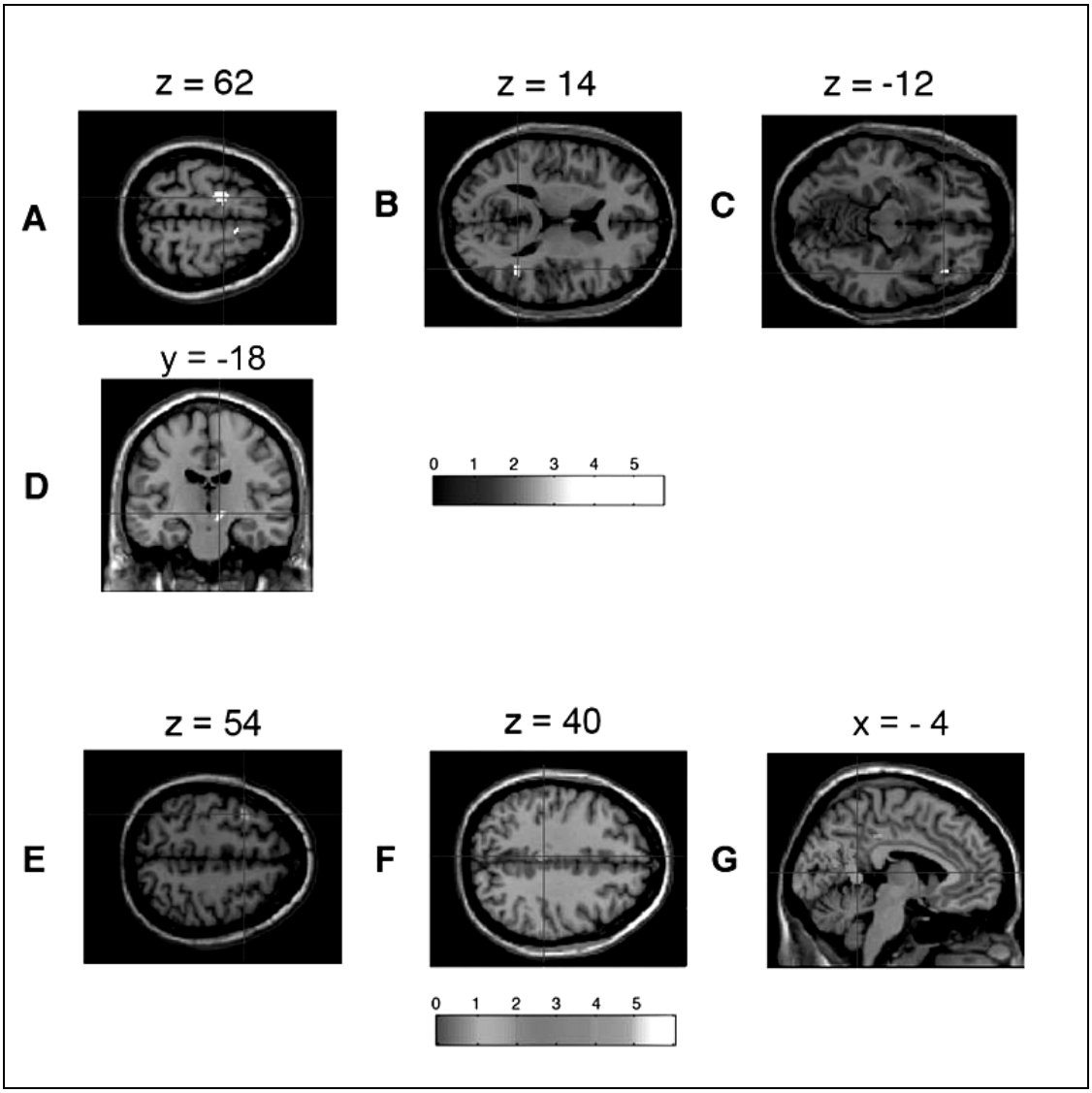

Figure 2. *Brain regions responding in correlation with preferences during the anticipation phase of winning trials.* (A) Bilateral mesial premotor / supplementary motor area showing most powerful activations, (B) right superior temporal sulcus, and (C) right anterior insula / lateral orbitofrontal cortex with significant activation patterns at uncorrected level of $p < .001$ with clusters with more than 10 voxels. (D) A cluster of midbrain activation was found at a close to significant level after small volume correction at threshold level $p < .01$. Neural activity in brain regions negatively linearly modulated by the brand preference (i.e., showing less activity for more preferred brands) during the anticipation phase: (E) left frontal middle gyrus, (F) left posterior cingulate cortex, (G) left precuneus.

Regions responding in correlation with preferences during the outcome phase of won winning trials

In the outcome phase of won winning trials, clusters of voxels in the following regions increased their hemodynamic response linearly with higher subjective preference for the reward (WOW1): The right precuneus, right supramarginal gyrus, left and right lingual gyrus, left posterior cingulum, right caudate nucleus, right superior temporal sulcus, right postcentral gyrus, right and left cerebellum including the vermis, left middle temporal gyrus, left superior occipital areas, right frontal inferior operculum, right superior frontal area, left angular gyrus and the right ventral pallidum (Figure 3, Table 3).

Table 3. Clusters with preference-dependent activity during the outcome phase. All clusters show a probability of error of $p < .001$ uncorrected for whole-brain multiple comparisons. The coordinates and t values are at the peak voxels in each cluster (coordinates refer to MNI-space). Clusters written in bold letters are within a priori hypothesized regions and are below a significance threshold of $p < .05$ family wise error corrected for small volumes (sphere with 8 mm radius).

Neural activity of regions increasing linearly with subjective preference:	Right/ Left	Cluster Size (Voxels)	Coordinates			t-value
			X	Y	Z	
Caudate nucleus	**R**	**51**	**18**	**8**	**18**	**5.19**
Caudate nucleus	**R**		**16**	**2**	**26**	**4.92**
Ventral pallidum	**R**	**82**	**24**	**2**	**-8**	**4.28**
Precuneus	R	200	6	-46	6	5.88
Posterior cingulum	L		-2	-42	8	5.21
Vermis	L/R		0	-54	-4	4.24
Precuneus	R	24	16	-60	40	5.25
Lingual gyrus	L	187	-20	-72	-4	5.29
Lingual gyrus	L		-14	-82	-12	4.89
Lingual gyrus	L		-12	-80	-2	4.68
Superior occipital	L	16	-14	-96	20	4.47
Lingual gyrus	L	16	-14	-56	0	3.90
Lingual gyrus	L	29	-6	-66	4	4.03
Lingual gyrus	R	74	22	-90	-16	4.82
Inferior occipital gyrus	R		34	-22	-16	3.74
Lingual gyrus	R	35	22	-52	-2	4.40
Lingual gyrus	R		14	-50	-4	4.26
Cerebellum crus1	R	140	16	-82	-28	4.62
Cerebellum crus 1	R		6	-20	-22	4.34
Cerebellum crus 1	L	20	-22	-66	-34	4.22
Superior temporal gyrus	R	19	52	-26	16	4.90
Supramarginal gyrus	R	62	42	-42	22	5.57
Supramarginal gyrus	R	13	46	-28	28	4.49
Middle temporal gyrus	L	13	-38	-56	16	4.55
Angluar gyrus	L		-42	-52	22	3.98
Postcentral gyrus	R	13	38	-30	54	4.86
Frontal inferior gyrus, triangular part	R	14	28	16	20	4.16
Superior frontal gyrus	R	12	18	28	40	4.15

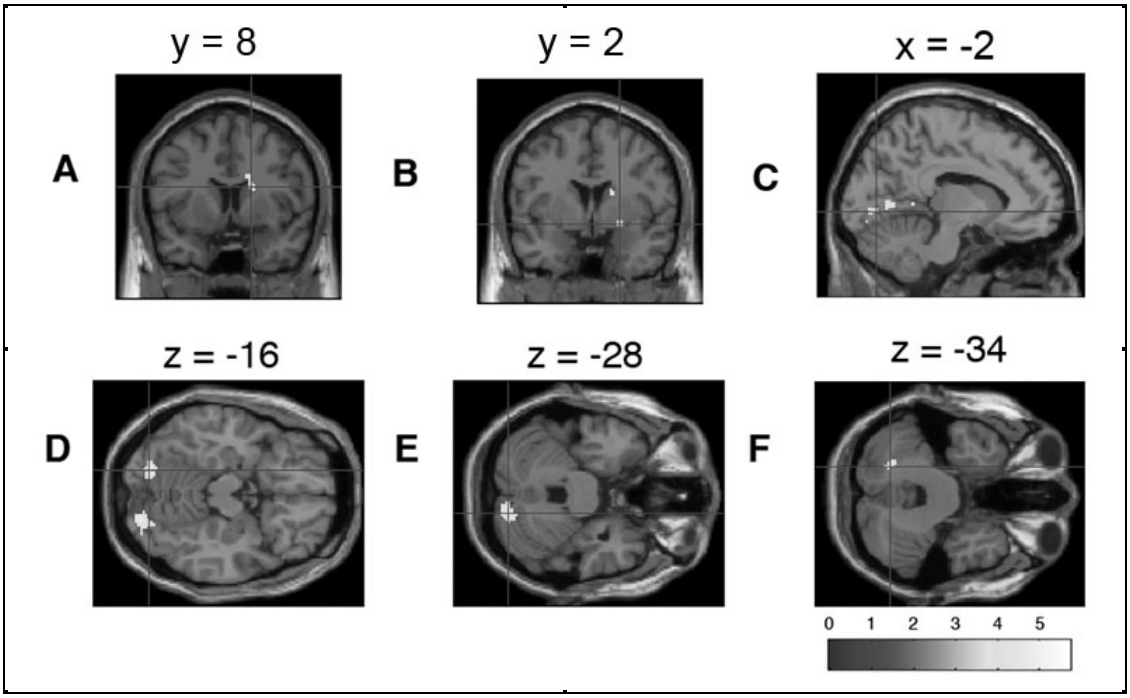

Figure 3. *Brain regions responding in correlation with preferences during the outcome phase of won winning trials*. (A) Caudate nucleus, (B) pallidum, (C)/(D) lingual gyrus, (E)/(F) cerebellum crus 1.

The analysis revealed no significant clusters of voxels with a linear decrease in activity to the parameter of subjective preference (WOW1).

5.1.5 Discussion

The anticipation of acquiring desired objects plays an essential role in everyday life. There are clear interindividual differences in the preferences for choice alternatives, be it in connection with fashion, food, or cars. However, it is unclear whether subjectively defined preference levels (e.g., most preferred brand) are differentially reflected on the neural level across individuals. Therefore, the purpose of the present study was to investigate brain areas that are sensitive to subjective reward intensity. For this purpose, we evaluated the neural activation patterns associated with the expectation and evaluation of receiving desired compared to less desired objects. A further aim of this study was to examine whether the modulation of neural activity by the intensity of brand attractiveness was evident in a distinct neural network during the anticipation of the desired objects and during the evaluation of the game outcome. Using a wheel-of-fortune game, we found that the hemodynamic responses in the

premotor cortex, the lateral orbitofrontal cortex, the insula, and the dopaminergic midbrain are linearly correlated with the subjective preference of a desired object. Such areas were most strongly activated while the participants expected to win the most desired object. In addition, the hemodynamic responses in the left middle frontal gyrus, posterior cingulate cortex and several extrastriate visual areas were negatively correlated with the expectation to win a desired object. In the ensuing outcome phase, while participants evaluated the positive game outcome, a distinct neural network commonly associated with attentional processes, sympathetic arousal, and cognitive-emotional evaluation of rewards showed preference-modulated activity.

Anticipation phase of winning trials

The most striking finding of our study is a linear increase in hemodynamic responses in the left caudal and rostral premotor cortex the more participants desired to win a chocolate bar. Previous studies also found reward-dependent activation in premotor areas. It was, for example, reported that premotor regions become more active with increasing monetary reward in a target detection task [24]. Also, in non-human primates, dorsal but also lateral prefrontal regions including the premotor cortex were rendered active while expecting rewards [29]. Furthermore, Roesch and Olson reported increasing activity in premotor neurons in macaque brains dependent on the value of a predicted reward [30]. In contrast to these studies, reward delivery in our study did not depend on an instrumental motor action (e.g., grasping a reward). Thus, a simple motor preparation account is not sufficient to explain our finding. We interpret the increase in bilateral premotor activity as an increased state of motor preparedness, which may facilitate approaching behaviour. It is conceivable that the modulation of motor preparedness by different values of subjective brand preferences occurs automatically due to action-inducing characteristics of such incentive stimuli. In a low-involvement, buying situation increased premotor activity could already be sufficient to "tip the scales" so that a person snatches at one product without making a conscious decision to do so.

The reduced hemodynamic responses in the left MFG in anticipation of winning a more preferred chocolate bar may reflect the functional antagonist to the increased premotor activity. In a meta-analytic study, Rubia and colleagues. report that this area (besides others) is activated in several Go/No-Go tasks – a task demanding high-level

cognitive functions of decision-making, response selection and response inhibition [31]. When playing for a more preferred chocolate brand in our study, such cognitive control of motor functions may be reduced. Support for this idea comes from Deppe et al. who report decreased neural activity in the left hemispheric middle frontal gyrus when participants imagined making binary decisions between a target brand, which was the market leader, and another (less popular) brand, as compared with choices between two less popular brands [16]. In another recent study, Schaefer and Rotte found reduced activation in a right hemispheric homologue when participants saw attractive car brands compared to less attractive car brands [32]. Both research groups concluded that rational thinking might be reduced when confronted with favoured brands.

In summary, the pattern of activity in the above mentioned neural network indicates an increased state of motivation for motor action (e.g., facilitating approaching behaviour). But what inherent properties of an object make it more desirable (so that it will be approached more frequently) than others? The increased hemodynamic responses in the right anterior insula / lateral orbitofrontal cortex when playing for preferred chocolate brands may signal enhanced somatic arousal associated with a favourite reward. Supporting this idea, the right insula plays a prominent role in the somatic-marker hypothesis [33]. According to this hypothesis, insular activation provides a neural substrate of emotional feeling states arising from automatic somatosensory responses, making them available to cortical processing and conscious awareness. In line with this idea, Critchley and colleagues found right hemispheric activation in anterior insular and orbitofrontal regions associated with sympathetic arousal in a reward-related decision-making task [34]. The authors suggested that these two regions are modulated by changes in peripheral somatic states and involved in the flexible representation of reinforcement [35].

We discovered preference-modulated hemodynamic responses in mesolimbic regions in the right midbrain. Dopaminergic neurons in the midbrain reflect the incentive or motivational value of a future reward and are associated with a subjective state of wanting [23, 36]. Additionally, studies with non-human primates demonstrated increased firing rates in dopaminergic midbrain neurons during the anticipation of rewards after associations between predictive cues and reinforcers have been learned [37]. In the case of the chocolate brand logos that we used, the association between

the predictive cues (i.e., the logos) and reinforcers (e.g., delicious chocolate) has likely been established by previous learning experiences of our participants.

The cluster of preference-modulated activity in the right anterolateral intraparietal region, which extends into the superior temporal sulcus (STS) probably reflects the process of inferring from the motion of the wheel whether the trial will be won or not; the higher the incentive value of the reward, the more relevant is this prediction. In previous studies, increased activity in this area was assumed to reflect action-outcome prediction through observation [38, 39]. Furthermore, the anatomical proximity to the parietal cortex, which has been found to be involved in visuo-spatial processing [40], underpins the notion that this area could be involved in the processing of spatial contiguity between current position and desired outcome position.

The negatively correlated neural activity (lower hemodynamic response, while anticipation more desired objects) found in regions encompassing the posterior cingulate gyrus, precuneus, lingual gyrus, fusiform gyrus and cerebellum may be due to task induced deactivation (TID). TID refers to a relative decrease in regional activity, as measured by blood flow or the blood oxygenation level dependent (BOLD) signal, during an active task compared to a "resting" baseline [41]. We believe that the decrease in the BOLD signal in the above mentioned neural structures refers to a higher externally cued cognitive involvement in the anticipation phase for more preferred brands compared to less preferred brands, resulting in a higher suppression of internally generated information processing. The study of McKiernan showed that TID increased with task processing demands [41]. TID often occurs in the posterior cingulate cortex extending dorsally into the precuneus [42, 43], but also in the precuneus and fusiform gyrus [41] and has repeatedly been found with higher magnitude in the left cortical hemisphere [42, 43, 44].

In summary, hemodynamic responses increased in areas associated with motor preparation, emotional tagging of stimuli, reward expectation and spatial attention when participants were in expectation of the outcome of the wheel-of-fortune game, while playing for a more desired item. Conversely, neural activity in structures, involved in stop inhibition of motor responses and internal information processing linearly decreased. While expecting the outcome, participants encountered an increased state of wanting (dopaminergic midbrain↑), external information processing (TID areas↓) and emotional tagging of the incentive stimulus (left anterior insula↑),

leading to a state of facilitated action induction (bilateral premotor cortex↑, middle frontal gyrus↓).

Outcome phase of won winning trials

In the time window after the participants saw the final outcome position of the wheel of fortune, preference-modulated activations were found in the caudate nucleus, precuneus, lingual gyrus, cerebellum, and, to a lesser extent, in the pallidum. Our results seem to reflect preference-dependent modulation of attentional processes, sympathetic arousal, and of cognitive-emotional evaluation of the reward value.

When participants were "rewarded" with more preferred chocolate bars, we found increased activity in the right caudate nucleus, traditionally seen as a "motor" region. Findings of Haruno et al. suggest, however, that the caudate nucleus is strongly involved in reward based behavioural learning [45]. It has further been shown in monkeys [29, 46] and rats [47] that part of caudate-putamen neurons respond to food and drink reward stimuli in a manner similar to dopaminergic or ventral striatal neurons.

The ventral pallidum (VP) has been suggested to represent a central relay station for the distributed brain circuit of core liking [17, 48], as well as a potential relay station to cortical systems of conscious pleasure [48]. Neurons in the VP are assumed to track the hedonic value of rewarding and appealing stimuli [49, 50]. Besides the more native activation of "liking" structures via taste reward and sexual- and competitive arousal, it has been shown that more abstract pleasures like monetary rewards also increase activity in the VP [18].

In the outcome phase many occipito-parietal regions, like the precuneus and parts of the lingual gyrus where found to be more active when winning a more preferred chocolate bar. We interpret this assembly of activations as a neural representation of top-down controlled visual attention. Playing for more preferred compared to less preferred chocolate bars is likely associated with a higher interest in the game outcome, which might cause a stronger attention focus on the outcome situation (visual perception and processing of the outcome). A cue for top-down attentional orientation in the visual field could be provided by an early tagging of emotional stimuli as Schupp et al. inferred from recent EEG studies [51, 52, 53].

We found brand-preference-modulated activity also in the cerebellum, namely in the vermis and right-sided crus 1. In addition to the predominant role in motor functions, it has been shown that the cerebellum is involved in higher cognitive and emotional processes [54]. The cerebellum is also an important component of autonomic control functioning. In line with this idea, Critchley et al. found distributed cerebellar activations similar to ours when participants experienced states of arousal [55]. Regarding our study, we can only speculate that some altered states of arousal may have occurred when winning a highly desired compared to a less desired chocolate bar.

The interpretation of the activations in the superior temporal sulcus, middle temporal sulcus, supramarginal gyrus and postcentral gyrus, inferior frontal and superior frontal regions is somewhat difficult, since these regions are not known to be specifically involved in reward or feedback processing. Since the reward that participants received in this study was merely artificial in that they were reflected by the gain in chocolate bars summed up on an account, the increased activity in these regions could imply the processing of spatial information of the wheel of fortune (e.g., "what is the relation to the initial speed set and the position of the wheel when it stops?"). Alternatively, changes in cerebral blood flow may have been induced through a heightened state of emotional / autonomic arousal or through attentional processes.

Neuronal networks increasingly active with brand preference in the outcome phase have been commonly linked to feedback processing, bodily perception of pleasurable arousal, and visuo-spatial attention. Participants registered the feedback of winning a more preferred brand with increased visual attention (occipital cortex↑) leading to a positive pleasurable feeling (ventral pallidum↑) accompanied with a heightened state of arousal (ventral pallidum↑, cerebellum↑).

Limitations

One has to bear in mind that the neural activity found in our study reflects to a certain degree interactions of subjective preference and the experimental task. For example, our participants expected a reward with uncertainty. It has been repeatedly shown that the factor of incentive probability partly alters the involvement of the reward network [18] [56, 57]. A second, and in our view, important factor is whether participants actually receive immediate material or delayed symbolic reward, obtaining in the

latter case the reward only after conclusion of the experiment. In our study, participants received the won bars of chocolate after the experiment outside the scanner. This is important, considering that partly different brain activations were produced for instance in the study of O'Doherty in which participants received differently tasting liquids during the experiment [23], compared with studies in which participants were rewarded with money after the scanning procedure [3, 24, 58].

Hemodynamic responses in the lateral orbitofrontal cortex and the insula correlated with the subjective preference of the anticipated gain during expectation of the rewarding stimuli. Neural activity in the OFC is known to correlate with the incentive value of the expected reward [2]. The additional activations found in the insula support the idea that emotions and feelings are evoked in this phase. Some recent studies propose a functional dissociation between the lateral and mesial OFC activation. While the mesial OFC is most strongly involved during anticipation of rewarding stimuli, the lateral OFC seems to be more strongly activated when punishment or deficits are anticipated [59]. However, as winning trials were explicitly separated from loosing trials, the pattern of activation is unlikely to reflect engagement in anticipating losses or punishment rather than receiving rewarding stimuli.

Although we found activations within the OFC and the insula during the expectation of rewards, we did not find strong activations in other brain areas that have been shown to be activated in previous studies exploring reward-related brain activations (e.g., prefrontal cortex or nucleus accumbens, for a review, see [56]). However, as mentioned above, there are considerable methodological differences between our and the other studies. The most striking difference between our and previous studies is that we use differentially preferred incentives of the same product class and same price category. The rewards expected by a participant – and evaluated after the outcome of the wheel-of-fortune game – did not differ significantly in their magnitude of objective (e.g., monetary) value, solely in the magnitude of subjective value. Participants possibly wanted to win each trial and "liked" every won winning trial. The rewards are objectively the same (one bar of chocolate), the only difference being the subjective preference of the reward. Our aim was to identify the neuronal correlates of the subjective, culturally learned preference that may be regarded as having a modulatory impact on wanting and liking, and as influencing approach (in this case buying) behaviour in many ambiguous decision-making situations.

Conclusion

The results of our study clearly demonstrate that neural activation in reward processing structures is modulated by stimuli varying in subjective reward intensity. This modulation was evident in situations where participants anticipated a reward and in situations where participants evaluated a reward. Contrary to the winner-take-all hypothesis [16], neural activity was linearly associated with the subjective brand preference hierarchy, which is in line with studies using objectively varied amounts of money as rewards. Furthermore, distinct brand-preference-modulated areas were identified during anticipation and evaluation phases. When participants anticipate winning a more preferred brand they experience an increased state of wanting. This is characterized by intensified processing of external information and emotional tagging of the incentive stimulus, leading to a state of facilitated action induction. Thus, the pattern of activity may reflect approach behaviour in real life situations, such as opting for a particular product on the shopping shelf.

5.1.6 Supplementary Data

Supplement 1

Table of significantly linearly modulated structures in the anticipation of losing trials. All clusters show a probability of error of $p < .001$ uncorrected for whole-brain multiple comparisons. The coordinates and t-values are at the peak voxels in each cluster (coordinates refer to MNI-space).

Regions	Right/ Left	Cluster Size (Voxels)	Coordinates			t-value
			X	Y	Z	
Increasing linearly with subjective preference						
Caudate nucleus	R	28	10	24	10	5.32
Caudate nucleus	L	26	-12	18	16	4.83
Decreasing linearly with subjective preference						
Calcarine sulcus	L	747	0	-90	14	6.07
Superior occipital cortex	L		-10	-100	24	4.36
Cuneus	L		-6	-100	16	5.67
Lingual gyrus	R	42	12	-62	-2	4.25
Lingual gyrus	R		2	-68	-6	3.46
Lingual gyrus	R		16	-54	-8	3.17
Temporal pole superior	R		60	8	-10	3.45

Table of significantly linearly modulated structures in the outcome of lost losing trials. All clusters show a probability of error of $p < .001$ uncorrected for whole-brain multiple comparisons. The coordinates and t-values are at the peak voxels in each cluster (coordinates refer to MNI-space).

Regions	Right/ Left	Cluster Size (Voxels)	Coordinates			t-value
			X	Y	Z	
Increasing linearly with subjective preference						
Inferior frontal operculum	R	19	24	8	14	4.98
Posterior cingulum	L	20	-18	-42	20	4.85
Decreasing linearly with subjective preference						
Middle frontal gyrus	L	26	-28	22	44	4.85

Supplement 2

Table of Main effects of the anticipation phase of winning trials (WA). All clusters show a probability of error of $p < .001$ uncorrected for whole-brain multiple comparisons. The coordinates and t-values are at the peak voxels in each cluster (coordinates refer to MNI-space).

Regions	Right/ Left	Cluster Size (Voxels)	Coordinates			t-value
			X	Y	Z	
Lateral occipital Cortex	R	5933	26	-94	-10	19.79
Lateral occipital Cortex	L	4151	-30	-96	8	13.97
Thalamus	L	291	-24	-30	-4	10.66
Thalamus	R	378	22	-28	-2	9.49
Caudate	L	58	-16	28	-4	5.33
Caudate	L	20	-22	-8	32	5.21
Lateral ventricle / Caudate	R	67	4	24	2	5.10
Brainstem	R	22	16	-28	-30	4.57
Lateral orbitofrontal Cortex	R	467	32	22	-26	6.37
Lateral orbitofrontal cortex	R	40	48	46	-16	5.11
Inferior frontal gyrus	L	491	-58	16	4	5.37
Inferior frontal gyrus	R	26	60	22	26	4.55
Superior frontal gyrus	R	14	30	4	68	4.06
Insula	R	11	44	-6	22	4.22
Premotor cortex	L	43	-22	-8	60	4.42
Premotor cortex	L	10	-40	-4	48	4.02
Precentral gyrus	R	116	38	-10	36	6.00
Postcentral gyrus	L	10	-60	-6	38	4.04
Cerebellum	R	23	12	-78	-46	4.49
Vermis	R	15	2	-34	-32	4.17
White matter / posterior corona radiata	L	12	-28	-30	28	4.29

Table of Main effects of the outcome phase of won winning trials (WOW). All clusters show a probability of error of $p < .001$ uncorrected for whole-brain multiple comparisons. The coordinates and t-values are at the peak voxels in each cluster (coordinates refer to MNI-space).

Regions	Right/ Left	Cluster Size (Voxels)	Coordinates			t-value
			X	Y	Z	
Occipital cortex	R/L	14927	-8	-86	-12	11.34
Parieto-occipital cortex	L	2119	-48	-60	30	9.45
Precuneus	R	13	2	-62	62	4.51
Caudate	L	236	-14	0	28	6.08
White matter / Caudate	L	12	-12	14	22	5.23
Caudate	R	27	14	14	20	5.22
Hippocampus	R	13	28	-32	8	4.91
Parahippocampal gyrus	L	17	-34	-12	-24	5.01
Middle frontal gyrus	L	174	-38	8	44	6.79
Middle frontal gyrus	R	211	40	26	24	6.07
Inferior frontal gyrus	L	526	-50	28	0	6.29
Superior frontal gyrus	R	119	2	28	62	6.15
Frontal Pole	R	48	44	52	-10	5.74
Middle frontal gyrus	R	73	42	18	48	5.68
Frontal Pole	L	33	-2	62	26	5.63
Orbitofrontal cortex	L	46	-34	22	-26	5.50
Frontal pole	L	13	-6	64	-2	5.38
Dorsomedial prefrontal cortex	R	83	18	48	48	5.28
Premotor cortex	L	158	-10	14	68	6.36
Premotor cortex	R	20	38	-20	68	4.89
Posterior cingulate gyrus	R	722	4	-46	34	5.43
Middle temporal gyrus	R	2422	68	-32	-8	9.20
Temporal pole	R	113	52	16	-22	6.40
Temporal Pole	L	12	-54	4	-26	5.54
Middle temporal gyrus	R	18	62	-4	-26	5.18
Temporal pole	L	16	-40	16	-34	5.07
Temporal pole	R	33	38	18	-42	4.33
Temporal fusiform cortex	L	10	-44	-40	-22	4.92
Precentral gyrus	R	69	64	-2	10	4.62
Postcentral gyrus	R	327	10	-38	74	7.06
Postcentral gyrus	L	30	-12	-42	74	5.46
Parietal operculum	R	55	46	-8	18	6.46
Parietal operculum	L	130	-26	-30	20	6.06
Parietal operculum	R	45	40	-26	26	5.40
Cerebellum	R	29	28	-76	-50	5.41
Cerebellum	-	27	0	-72	-46	5.30
Cerebellar tonsil	R	12	10	-56	-36	3.92
White matter/ putamen	R	108	32	-2	24	5.07
Genu of corpus callosum	L	191	-2	24	8	6.58
Intraparietal Gyrus	R	46	24	-54	36	4.54
White matter / premotor cortex	R	11	24	-22	44	4.31
Lateral ventricle	R	13	6	-30	16	4.25

5.1.7 References

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5.2 Experiment 2, Part 1: Brand preferences modulate neural activity during motivational and evaluative reward components.

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5.2.1 Summary

Humans may differ remarkably in their preferences for objectively similar rewards. Brand preferences, for instance, largely account for differences in shopping behaviour. The current functional MRI study explores whether subjective brand preferences can be measured on the neural level. For this purpose, a wheel-of-fortune game comprising a prospect phase and a subsequent outcome evaluation phase was implemented. Participants played for vouchers for sneakers of three different brands that differed in subjective attractiveness. The results clearly demonstrate that neural activation in structures related to reward processing is linearly associated with the subjective brand preference hierarchy. Further, modulation of neural activity by preferred brands occurs in distinct neural regions during prospect and evaluation phases. Playing for more preferred compared to less preferred brands evokes an intensified state of wanting in the participant and facilitates action preparation - a mechanism that may underlie approach behaviour in real life choice situations.

5.2.2 Introduction

To account for variance in people's choices, social scientists have introduced the concept of preferences. Based on the idea of utility maximization, the concept of preferences allows for assigning individually different utility values to outcomes, and is thus used to explain why people may be motivated by different incentive stimuli. With the advent of modern brain imaging techniques the neural underpinnings of motivational processing has received considerable interest. For example, it is well explored how reward-value associations are learned and dynamically updated in non-human primates and humans [1][2]. Also the neural underpinnings of contextual

influences on reward values, like counterfactual reasoning [3], the effect of framing [4], satiety [5] and delay discounting [6] have been a matter of extensive research. However, the factor of subjectiveness of rewarding values – that is, subjectiveness of preferences – has rarely been investigated. In the current study, using branded products as an economically highly relevant example, we explore whether the factor of subjective preferences can explain differences in neural responses to rewarding events.

In a previous study we were already able to show that stimuli with objectively similar characteristics elicited hemodynamic responses in reward related areas of the brain in dependency of the respective preference value [7]. Participants played a wheel-of-fortune (WOF) game, where they could win or lose chocolate bars that differed in subjective value. Subjective value was operationalized in terms of brand preferences, which were a priori measured with state-of-the-art market-research tools. Given that brand preferences greatly differ between individuals and the objectively scaled values of related consumer goods (like price and quality) are often highly similar, we believe that such stimuli are ideal to investigate the variation of rewarding value on a subjective scale. Indeed effects of branding on activity in reward-related brain areas have been reported before [8]. For example, it has been shown, that the consummation of small amounts of soft drinks elicited stronger hemodynamic responses in reward related areas of the brain, when pre-cued by a logo of the market leader, rather than by a logo of another soft drink manufacturer [9]. To our knowledge, this effect however was not described for individual brand preference hierarchies before.

The choice of chocolate as reward in the previous study had the advantage to incorporate a primary reinforcer, which has been shown to reliably elicit strong activations in reward-related brain regions [10]. One potential drawback of investigating subjective values of primary reinforcers is that the rewarding value of food is highly dependent on satiety [5]. It is assumable that this effect applies even if no direct food intake occurs, as it was the case in our last study. Furthermore, the preferences for one particular brand of chocolate might be more influenced by the flavour of one specific bar of chocolate than by the brand itself. In the present study we aimed to extend previous findings by using specific non-food rewards, for which it can be assumed, that subjective value is independent of the degree of satiety as well as primary sensory qualities such as flavour. We therefore chose fashion products for which we presume that subjective value is predominantly culturally transferred and

were interested in whether we can replicate the results found for chocolate brands. Also, the incentives used in the present study (a 150 SFr. voucher for a pair of sneakers of a particular brand) were monetarily much more valuable than what could be won in the initial study (on average around 10 bars of chocolate). By increasing the monetary incentive value, we aimed at also increasing the effects of subjective preferences for different brand versions of this incentive. Finally, besides changing the product class of the rewarding stimuli, modifications in the reward scheme were applied. In the previous study chocolate bars of three differentially preferred brands could be won or lost. Thus, a once gained reward could be lost in any subsequent trial. Alike, the probability to acquire a reward only increased towards the very end of the experiment. In the present study subjects could increase the probabilities for winning differently valued rewards, rather than accumulating (and loosing) rewards during the actual experiment. Therefore, reward values in every single trial were kept constant over the time-course of the experiment. By comprising these refinements we aimed to replicate and strengthen the previously reported findings and extend insights to more abstract and culturally transformed subjectively valued rewards. Finally we were interested in comparing neural responses of the "accumulating probability" reward scheme to results of commonly used reward schemes like gaining primary reinforcers or accumulating monetary rewards

To address these issues, we used a wheel-of-fortune game that allowed for the differentiation between a prospect period (spinning of the wheel; wishing for a positive outcome) and an outcome period (processing the game outcome). During the fMRI session, subjects could win lottery tickets in repeated rounds of the wheel-of-fortune game, thereby increasing their chance of winning in the subsequent lottery. In the lottery, subjects played for one voucher worth Sfr. 150 for one of three different sneaker brands. Established market research instruments were used prior to the fMRI experiment to determine participants' individual preferences with respect to sneaker brands. Brands of high, intermediate and low subjective value were then selected for each participant and used as stimuli in the fMRI experiment. During the experiment, brands were represented by their logos. The rationale of our approach was that since the monetary value of each voucher was equal for the three brands, any elicited differences in neuronal activations could be exclusively attributed to differences in subjective value formed through individual brand preferences.

5.2.3 Methods

Participants

Sixteen healthy adult voluntary participants (9 female and 7 male, mean age of 24 ± 4) were recruited from the University of Zurich and ETH Zurich, Switzerland. Participants were selected based on a two-stage selection procedure. At the first stage, a paper and pencil questionnaire was distributed to students in different courses of the Psychology Department of the University of Zurich. 200 students completed the questionnaire. Of those, 50 respondents who indicated that they (a) wore sneakers at least from time to time, (b) cared about sneakers, (c) cared about brands when it came to sneakers, and (d) who expressed differentiated brand preferences in a constant sum point allocation "chip game" between different sneaker brands, were invited to the second round. Twenty-seven of the pre-selected participants accepted the invitation and filled in a second, computer-based questionnaire that aimed at measuring individual brand preferences in more detail with a choice-based procedure [11] and, again, with a constant sum chip game. Of those, eighteen respondents were finally invited to the fMRI study. These participants expressed preferences that were consistent across the two measures and widely dispersed to allow for clear brand differentiation. Two participants dropped out due to private reasons. The local ethics committee approved the study and the participants gave written informed consent. The tasks and testing procedures were in accordance with institutional guidelines and the study conformed to the Declaration of Helsinki. Participation was compensated with 50.00 sFr. and a possible win of a voucher for a pair of sneakers, worth 150 sFr.

Design and Procedure

Participants played a virtual wheel-of-fortune game projected onto a translucent screen that participants viewed inside the scanner via a mirror. The experiment consisted of four runs with 25 trials each. Individual T1-weighted anatomic brain images were recorded after the actual experimental sessions. The total scanning time was approximately 50 minutes.

Before being scanned, participants were informed with respect to the MRI / fMRI method. Following this, each participant had to (1) complete a questionnaire that

checked for individual MR-suitability and (2) to give his / her written informed consent. Then, participants were requested to read a short instruction manual, which explained the procedures of the experiment, and played two trials of the wheel-of-fortune game outside the scanner to assure that they had understood the task correctly. The overall prize that could be won in our experiment was a voucher (worth 150 SFr.) for a pair of sneakers of a particular brand. The subjects played for this voucher in a lottery subsequent to the scanning session. During the scanning session, the subjects were able to win lottery tickets that increased the chance of winning in the subsequent lottery. In other words, a won trial in the wheel-of-fortune game increased the probability of winning the voucher for a certain sneaker brand.

Based on the preference data gathered in the second stage of the selection procedure (see Participants section) 3 sneaker brands were determined for each subject: (1) her/his favourite brand, (2) her/his least preferred yet still acceptable brand, as well as (3) one intermediate brand that ranked between the top and the bottom brand. In each wheel-of-fortune trial one of 25 lottery tickets per brands could be won (i.e., 75 lottery tickets in total). Trials were brand-specific meaning that a won trial increased the chance to win a voucher for one specific brand. Across the scanning session, the number of won lottery tickets for each brand was accounted. After the scanning session, the subjects were presented with three pots (one for each brand), each containing 25 lottery tickets, with one lot being the joker. The subjects then drew the amount of won lottery tickets separately for each brand. If the joker was drawn, participants received the voucher for the particular brand. If more than one voucher was won, they could freely choose one to take home. The chance to win was pseudo-randomly varied at a chance of 50 percent. Thus, participants had the cumulative chance to win one of the three vouchers of 87.5 percent. The sequence of the brands the participants played for were pseudo-randomly distributed to ensure enough trials of every possible combination (brand, outcome) for the analysis. In addition, 25 trials where no lottery tickets could be won were randomly interspersed in the experiment to detect brain areas responding to the wheel-of-fortune game itself, resulting in a total of 100 trials.

As illustrated in Figure 1, a trial consisted of a brand announcement phase (0.5 – 2 s), a response phase (placing the bet on green or red; 1-2 s), a prospect phase (wheel of fortune spins; 8-12 s), an outcome phase (outcome is presented; 3 s), a blank screen with a fixation cross (4-5 s), a picture of the actual balance (2 s), and a blank screen

with a fixation cross (6 s). In the announcement phase the logo of the brand subjects played for in the current trial was presented in the center of a wheel-of-fortune with twelve colored (6 green and 6 red) fields. During the response phase, participants could choose one color by pressing a button. The chose color field remained visible underneath the wheel while the other color field disappeared so that participants did not have to memorize their choice. The prospect phase started with the wheel-of-fortune rotating and slowing down to halt after 8-12 seconds. The ensuing outcome-phase started after the wheel had stopped. The outcome was indicated by the field that came to a halt under a pin at the top of the wheel and by a text box (i.e., "You have won 1 lot / You have not won"). A trial was won when the color chosen by the subject was consistent with the color of the field that came to a halt under the pin. To prevent participants from memorizing account balances, the balance of the number of lottery tickets for the respective brand acquired so far was indicated in each trial. This number was also translated into the probability of winning a voucher and represented as bar chart. A blank screen with a fixation cross was presented for six seconds before the next trial started to ensure that the fMRI signal could level back to a task-unspecific baseline.

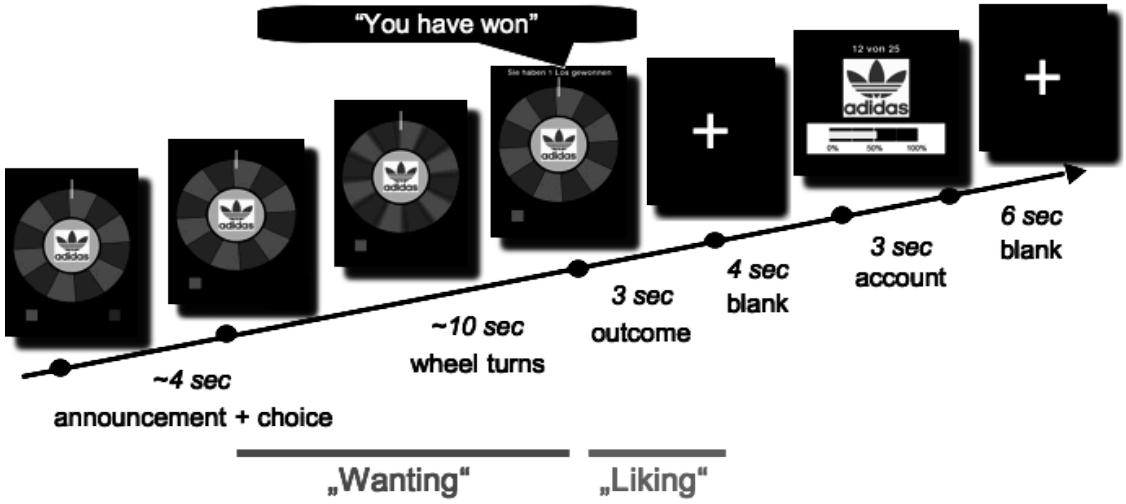

Figure 1. *Experimental design of the wheel-of-fortune game*.

Functional Imaging

A Philips Intera 3T whole-body MR unit (Philips Medical Systems, Best, The Netherlands) equipped with an eight-channel Philips SENSE head coil was used to acquire magnetic resonance images. Anatomical images of the whole brain were obtained by using a T1-weighted three-dimensional, spoiled, gradient echo pulse

sequence (repetition time (TR) = 20 ms, echo time (TE) = 2.30 ms, flip angle = 20°, field of view (FOV) = 220 mm, acquisition matrix = 224 x 224, voxel size = 1.00 x 1.00 x 0.75 mm, 180 slices, slice thickness = 0.75 mm). Functional data for the behavioural tasks were obtained from 310 whole-head scans per run using a Sensitivity Encoded (SENSE) single-shot echoplanar imaging technique (TR = 2500 ms, TE = 35 ms, flip angle = 78°, FOV = 220 mm, acquisition matrix = 80 x 80, 33 transverse slices, voxel size = 1.72 x 1.72 x 4.00 mm).

Data Analysis

Artefact elimination and MRI data analysis were performed using MATLAB 2006b (Mathworks Inc., Natick, Massachusetts, USA), and the SPM5 software package (Institute of Neurology, London, UK). The first three images were discarded to allow for steady-state magnetization. All images were realigned to the first image of the first run, slice time corrected and spatially normalized into standard stereotactic MNI space (EPI template provided by the Montreal Neurological Institute), interpolated to a voxel size of 2.00 x 2.00 x 2.00 mm and spatially smoothed using a 8-mm full-with-at-half-maximum Gaussian kernel.

Activated voxels were identified by the general linear model approach implemented in SPM5. At the first level of analysis, we adopted a parametric analysis according to Buchel et al. (1998). After highpass-filtering (cut off 128 s), an individual statistical model was computed for each participant with separate regressors for the announcement phase (1 s), response phase (1-2 s), anticipation phase (8 – 12 s), the two types of outcome phases (3 s) and the presentation of the actual balance (2 s). The announcement, response and anticipation phases and the blank screen between outcome and balance had variable durations. Also, the time-lag between motor response for choosing a color and the onset of the anticipation phase (the start of the spinning of the wheel-of-fortune) was temporally jittered. This was implemented to (1) induce a dephasing of stimuli onsets with respect to scan onsets to optimize sampling of the hemodynamic response and (2) to temporally de-correlate regressors of interest. The resulting regressors were convolved with SPM's canonical difference of gammas hemodynamic response function.

The analysis mainly targeted regions whose hemodynamic response was modulated by individual brand ranking. Thus, the individual ranking of the brands were

introduced into the statistical model as first and second order modulatory parameters of the regressors of the announcement, anticipation, outcome and balance phases. Subsequently, linear contrasts of the first and second order terms against a baseline (blank screens) were performed. This was applied to the announcement, anticipation, outcome, and actual balance phases. In order to dissociate task-specific effects of the wheel-of-fortune game and brand preference specific effects, neutral trials were implemented (see Design and Procedure), which were modelled as separate regressors for each phase.

To permit population-level inferences, maps of contrast coefficients for each of the first level contrasts were collectively submitted to one-sample t-tests against the null hypothesis of no increase in hemodynamic response, while controlling for random effects. Despite de-correlation of the anticipation and outcome phase through temporal jittering of the duration of the anticipation phase it was still possible that clusters of activation found in the outcome phase could be due to continuing activity elicited during the anticipation phase. Taking this possible confound into account, the search area for activations in the outcome phase was reduced to the areas activated by the preceding anticipation phase in an additional analysis. No clusters of activation remained.

To explore a wide range of effects in the data, voxels surviving significance thresholding at $p < .001$, uncorrected for multiple comparisons with a spatial extent threshold at $k = 10$ voxels were reported. For specific regions, a-priori hypotheses were derived from previous reward paradigms [10, 12-14]. Within these regions, small volume corrections (SVC) were applied to correct the false positive error probability for the number of made comparisons. SVCs were applied with a sphere of 8 mm, chosen to be equal to the spatial smoothing kernel [15]. Peaks surviving $p < .05$ family-wise-error (FWE) correction were considered significant.

5.2.4 Results

The primary goal of this study was to identify areas of the brain showing stronger hemodynamic responses, when playing for more preferred brands. We further examined whether distinct neural networks process reward information in the anticipation phase and the outcome phase of won trials. The following results represent the first order term in the parametric analyses.

Regions exhibiting preference-modulated neural responses during the anticipation phase

In the prospect phase, hemodynamic responses linearly increasing with higher subjective preference were identified in right anterior insula / lateral orbitofrontal cortex (OFC), left pallidum / nucleus accumbens, bilateral premotor cortex, supplementary motor area, right supramarginal gyrus, primary somatosensory cortex and bilateral precuneus. (Figure 2, Table 1).

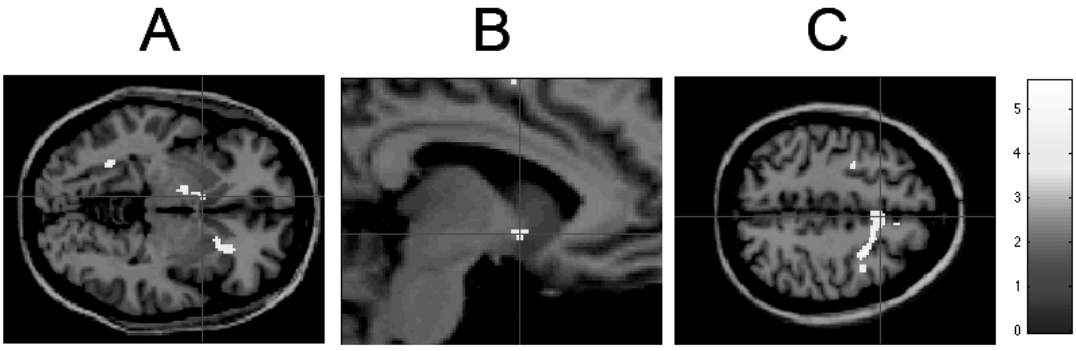

Figure 2. *Neural activity in brain regions linearly modulated by the brand preference (i.e., showing greater activity for more preferred brands) during the anticipation phase ($p < .001$ uncorrected*): (A) right hemispheric anterior insula. (B) Left nucleus accumbens. (C) Predominantly right hemispheric premotor cortex and supplementary motor area.

Table 1. Clusters showing brand-preference-dependent activity during the anticipation phase. Clusters with an error probability of $p < .001$ uncorrected for multiple comparisons are reported. The coordinates and t-values are at the peak voxels in each cluster (coordinates refer to MNI-space). All clusters written in bold letters are within a priori hypothesized regions and survive a significance threshold of $p < .05$ family wise error corrected for small volumes.

Neural activity in regions	Right/ Left	Cluster Size (Voxels)	Coordinates			*t*-value
			X	Y	Z	
increasing linearly with subjective preference:						
Anterior insula	**R**	**161**	**28**	**26**	**-2**	**4.98**
Superior frontal gyrus	R	41	38	44	26	5.21
Middle frontal gyrus	R	28	42	34	34	4.40
Nucleus accumbens / ventral pallidum	**L**	**121**	**-14**	**-4**	**-2**	**5.51**
Premotor cortex	**R**	**656**	**30**	**2**	**46**	**5.91**
Premotor cortex	**L**	**340**	**-28**	**-4**	**56**	**5.41**
Premotor cortex, pre-SMA	**R**	**137**	**12**	**8**	**64**	**4.83**
pre - SMA, paracingulate gyrus	**L**	**53**	**-10**	**6**	**52**	**4.95**
Supramarginal gyrus	R	100	56	-36	22	4.82
Supramarginal gyrus	R	32	48	-30	32	4.84
Broca area	L	36	-50	4	14	4.23
Superior parietal lobe	R	83	12	-54	66	4.82
Primary somatosensory cortex	R	112	32	-44	64	4.64
Lingual gyrus	L	51	-30	-56	-4	4.88
Precuneus	L	103	-8	-46	58	5.93
Precuneus	R	53	10	-74	42	3.84

Regions exhibiting preference-modulated neural responses during the outcome phase of won trials

In the outcome phase of won trials, clusters of voxels in the anterior prefrontal cortex and anterior cingulate cortex (subgenual part) increased their hemodynamic response linearly with higher subjective preference for the reward (Figure 3, Table 2).

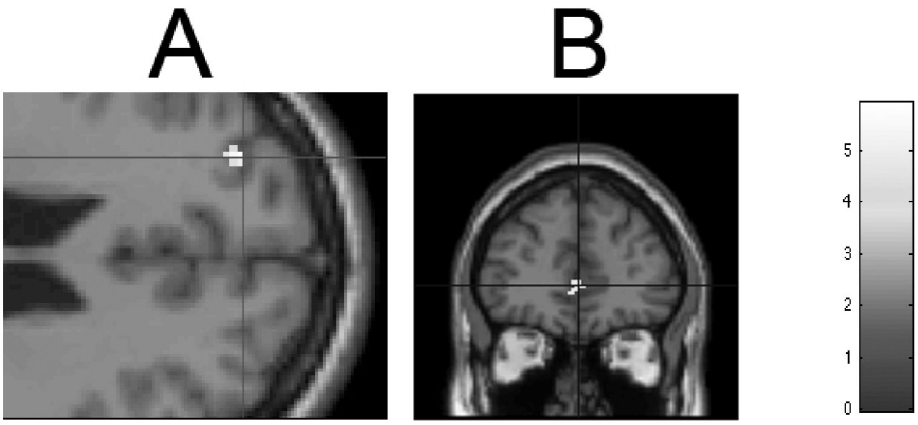

Figure 3. *Brain regions responding in correlation with preferences (i.e., showing greater activity for more preferred brands) during the outcome phase of won trials (p < .001 uncorrected).* (A) dorsolateral prefrontal cortex (DLPFC), (B) mesial prefrontal cortex (VMPFC).

Table 2. Clusters with a significant activity of p < .001 uncorrected for whole brain multiple comparisons are reported. The coordinates and t-values are at the peak voxels in each cluster (coordinates refer to MNI-space). All clusters written in bold letters are within a priori hypothesized regions and survive a significance threshold of p < .05 family-wise error corrected for small volumes.

Neural activity of regions	Right/ Left	Cluster Size (Voxels)	Coordinates			*t*-value
			X	Y	Z	
increasing linearly with subjective preference:						
Dorsolateral prefrontal cortex	**L**	**163**	**-26**	**50**	**24**	**5.64**
Mesial prefrontal cortex	**R**	**16**	**2**	**44**	**2**	**4.27**

5.2.5 Discussion

The aim of this study was to replicate and strengthen the findings of our previous study [7] that explored brain areas responding to rewards differing in subjective value. For this purpose, we used sneaker brands as rewards that differed in subjective attractiveness, following the hypothesis that brands have the power to modulate the subjectively perceived value. In line with the results of our former study, we were able to demonstrate that playing for more preferred rewards compared with less preferred rewards induces increased neural activation in structures commonly linked to reward processing. Results furthermore suggest the proposed distinction between

anticipatory and evaluative aspects of reward processing [14]. Thus, results seem to generalize across different reward categories. In addition, we could show, that increasing one's chance of obtaining a reward elicits neural activity comparable to winning primary reinforcers or accumulating monetary rewards.

Anticipation phase

"The anticipation of a reward is thought to lead to motivated behaviour through a series of steps originating in the limbic system and terminating in the motor system" [16]. Our results revealed neural structures along this pathway. Thus, the increase of the incentive value of the sports shoes induced by more preferred compared with less preferred brands is reflected by enhanced activity of neural structures commonly associated with reward processing.

While participants were waiting for the outcome of the spinning wheel-of-fortune, hemodynamic responses in the left ventral striatum were linearly associated with subjectively perceived reward value. The ventral striatum is known to be involved in the prediction of rewards in terms of expected reward value and expected reward probability [17]. Given that in this study, between-trials reward probability was held constant across trials ($p = 0.5$), the preference-modulated activation of the ventral striatum likely reflects the augmented value that a more favoured brand adds to an expected reward. In a majority of studies that have used monetary reinforcers, a similar relation between neural activity and reward magnitude has been reported [18]. In contrast, a study of Elliott et al. (2003) [13] showed a non-graded striatal response to varying monetary rewards. This contradictory finding might be due to the fact that reward anticipation and reward outcome were not modelled as separate conditions but analyzed in a blocked design. It was shown previously that this distinction is important: Using single cell recordings in primates' midbrain dopaminergic neurons, Tobler et al. (2005) [19] , for example, demonstrated that the spiking response to a reward cue is sensitive to the magnitude of the expected reward value but not the response to the reward outcome. In line with this finding, Cromwell and Schultz (2003) [20] reported a monotonic relationship between discharge rates of primate striatal neurons and expected reward magnitudes. Thus, we assume that the activation in the ventral striatum in our study reflects expectancies concerning the predicted,

forthcoming reward value and clearly indicates that this value is modulated by the subjective value associated with specific brands.

Our analysis further revealed a cluster in the right anterior insula to respond to the subjective value of the rewards played for. While activity in the insula has been traditionally associated with negative emotional states, arising in response to aversive stimuli such as facial expressions of disgust [21], pain [22] or monetary losses [23] it is also reliably responding to monetary gains [24] and appetitive processing [25]. In addition, results of recent lesion studies demonstrated that smokers with damage to the insular cortex no longer experience conscious urges to smoke after quitting, suggesting that the insular cortex is a key structure in the perception of bodily needs that provides direction to motivated behaviours [26]. Taking the above mentioned findings of previous studies into account we cannot definitely answer the question whether reward value dependent insular activity can be attributed to positive emotions in the anticipation phase. It is equally conceivable that the preference-modulated activity in the anterior insula may be due to the potential risk of reward omission which probably is regarded as more negative in case of more preferred brands.

In addition to the ventral striatum and the insula, a monotonic reward-value dependent increase of the hemodynamic responses was registered bilaterally in the premotor cortex and pre-SMA. Given that reward delivery did not depend on an instrumental motor response (such as grasping for a reward), processes of motor preparation or motor execution [27] cannot explain this finding. Instead, premotor activity and pre-SMA activity may represent an increased state of motor preparedness, which may be the result of action-inducing characteristics of incentive stimuli. It is likely that the premotor cortex activity and pre-SMA activity reflect motivational modulation of motor signals corresponding to the value of a reward (i.e., increased motor preparedness for more desired rewards), as previously shown in primate single cell studies [16] and human brain imaging studies [7, 13, 18].

Outcome Phase

In each trial, when the wheel of fortune game stopped, the participants were informed as to whether they had won or not. In trials in which participants won, hemodynamic responses in the dorsolateral prefrontal cortex (DLPFC) were stronger for more preferred brands. This is line with the findings of McClure et al. (2004) [9], showing

that participants' previously expressed brand preferences influenced neural activity in the DLPFC during subsequent consumption of soft drinks. The DLPFC is understood to play an integrative role in cognitive control [28] and short-term memory processing [29]. Additionally, results from studies with patients with major depressive disorders and patients with DLPFC lesions [30] suggest an involvement in affective and motivational processing.

Hemodynamic responses in the mesial prefrontal cortex (VMPFC) also correlated with brand preferences in the outcome phase. A large number of studies reported increased hemodynamic responses in the VMPFC when participants received information about gains compared with no gains or losses. This holds for primary reinforcers, such as drinks [9] and for secondary reinforcers, such as money[14]. Knutson and Peterson therefore propose that the MPFC tracks the experienced utility of rewards [31]. Furthermore, MPFC activations were found irrespective of whether the rewards were consumed immediately (e.g. liquid food: [10]) or obtained after the experimental procedure (e.g., monetary rewards [12]). It should be noted that participants in our study did not accumulate money over trials, but could only increase the probability of winning a voucher of a given value for a particular brand. Thus, the reward value perceived in each winning trial of our study is affected by the subjective brand preference but also by reward probability defined as the number of won lottery tickets at a given point in time. To overcome the problem that people often experience difficulties with cognitively processing probabilities [32], probabilities were represented by frequencies (of lottery tickets) in our study, which are easier to understand [33]. But despite the more abstract reward scheme, our results are comparable to those of studies in which guaranteed monetary rewards were collected [34]. Thus, the results seem to hold regardless of whether expected reward value is manipulated by changing the value of the outcome or by changing its probability. Besides its prominent role in processing the value of obtained rewards, MPFC activation has also been observed in the context of emotional arousal and introspection [35-37]. Overall, findings of past research and of the current study indicate that the MPFC is involved in the evaluation of reward-magnitude and reward–valence, largely independent from sensory modality and the degree of abstraction.

Differences to the findings of the study of Koeneke et al. 2008

One major goal of the present study was to replicate and extend previously reported findings of a study of our group [7]. The foremost modifications of the present study compared to the former implied an altered reward scheme (participants could increase reward probabilities rather than gain – as well as lose – rewards) and the use of different rewards (sneakers rather than chocolate bars). Overall, similar structures were inferred from the analysis, suggesting reliable activation of reward related brain structures to differentially valued rewards.

In the previous study we did not find value-related activity in the ventral striatum. This incongruency to the present results is likely due to differing reward schemes. In the former study participants could subsequently win and lose rewards. Thus, the expected reward value might have been minimized because the probability to keep a once gained reward over the whole experiment was small. Supporting this notion, a recent fMRI study demonstrated that neural activity in the ventral striatum correlates with the expected probability for a reward [38]. In contrast, the reward scheme applied in the present study implied an irreversible accumulation of chance to win one out of three differentially preferred rewards. Each lot to be won represented an increase in chance over the whole experiment and therefore the perceived reward value was likely higher, than in the previous study. At the same time, the monetary value of the likely reward was higher (a voucher worth 150 SFr., won with a probability of $p = 0.5$ per brand, resulting in an overall win probability of $p=0.875$). Compared to the average gain of 10 chocolate bars in the previous study, the stakes were higher in the current study, which may have further contributed to strengthening the effects.

In the present study participants could win vouchers for a pair of sneakers of a specifically preferred brand. Marketing in this product category mainly focuses on associating the brands with a certain lifestyle rather than advertising concrete product features [39]. In addition, up-market sneakers are similar in price, appearance and quality. Thus, we believe that the subjective values for the differentially preferred vouchers are predominantly culturally transferred. On the other hand, chocolate bars of different brands employed in the previous study possibly posed a less culturally influenced reward category. Preferences for chocolate might be more influenced by preferences in taste than the preference for the brand. Given, that in both studies,

highly similar structures of the brain (besides the ventral striatum) responded to differences in subjective value, it is conceivable that brain areas of the reward system generally respond according to perceived subjective values of rewards, irrespective of the reward stimulus category (eg. primary reinforcers such as tasty food, monetary rewards, or other secondary reinforcers with culturally transferred meaning) and the degree of abstraction of a reward (e.g. accumulating chances to gain a reward, accumulating rewards).

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5.3 Experiment 2, Part 2: Differential Magnitude Coding of Gains and Omitted Rewards in the Nucleus Accumbens

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5.3.1 Summary

Physiologic studies revealed that neurons in the dopaminergic midbrain of non-human primates encode reward prediction errors. It was furthermore shown that reward prediction errors are adaptively scaled with respect to the range of possible outcomes, enabling sensitive encoding for a large range of reward values. Congruently, neuroimaging studies in humans demonstrated that BOLD-responses in the ventral striatum encode reward prediction errors in similar fashion as dopaminergic midbrain neurons, suggesting that these BOLD-responses may be driven by dopaminergic midbrain activity. However, neuroimaging results are ambiguous with respect to the adaptive scaling of reward prediction errors, leading to the conjecture that under certain circumstances other than dopaminergic midbrain input may drive ventral striatal BOLD-responses. The goal of this study was to substantiate whether BOLD-responses in the ventral striatum rather respond to adaptively scaled reward prediction errors or absolute reward magnitude. In addition, we aimed to identify neuronal structures modulating activity in the ventral striatum. Sixteen healthy participants played a wheel of fortune game, where they could win three differently valued rewards while being scanned. BOLD-responses increased after gaining rewards; this gain was however independent of the absolute reward magnitude. In contrast BOLD-responses upon reward omission decreased with reward magnitude. A psychophysiological interaction analysis identified a cluster in the brainstem in proximity of the dorsal raphe nucleus, a cluster in the lateral orbitofrontal cortex, and a cluster in the rostral cingulate zone. These clusters changed their connectivity with the ventral striatum in relation to the absolute reward magnitude in reward omission trials.

5.3.2 Introduction

Seminal experiments have demonstrated that dopaminergic midbrain cell firing patterns are related to reward processing, in particular to the encoding of the difference between expected reward and experienced reward, thus represent reward prediction errors (RPE) (for a review see Schultz, 2000). It has been shown that RPE's are modulated by means of the expected probability, delay of occurrence and the magnitude of the reward (Fiorillo et al., 2003; Schultz et al., 1997; Schultz, 1998; Tobler et al., 2005). It has been furthermore demonstrated that dopaminergic RPE-signals are scaled with respect to known alternatives (Tobler et al., 2005). Specifically, the authors established that when three cues predicted pairs of rewards of different magnitudes, the better outcome always elicits the same positive reward prediction error signal, irrespective of the absolute reward magnitude. This scheme also applies to negative outcomes that are followed by the same negative RPE-signal. As a consequence of this "gain adaptation" the neural response discriminates equally well between two potential outcomes, regardless of their absolute differences in magnitude. In this manner, the ability to sensitively encode rewards is maintained over a large range of reward values (Tobler et al., 2005).

A recent study of Bunzeck et al., (2010) investigated adaptive coding of RPE's in humans using functional magnetic resonance imaging (fMRI). Similar as in the study of Tobler et al. (2005) subjects were presented three different cues, which predicted two rewards with different magnitude but identical probability. They could elegantly demonstrate that (blood oxygenation level dependent) BOLD-responses in common target areas of the dopaminergic midbrain such as the ventral striatum reflect scaled adaptive coding of reward prediction errors, such that irrespective of the difference of the absolute magnitude, the better outcome elicits the same increase in BOLD response compared to the lesser outcome. Thus, it was shown that BOLD-responses in the ventral striatum encode reward magnitudes with respect to the known alternatives and not at an absolute scale. Many other studies investigated BOLD-responses to differentially rewarding (and punishing) outcomes, although not with the specific goal to investigate "gain adaptation". If different rewards (which are fully known to the subject) can be won or lost, prediction errors should be scaled to the absolute difference between winning and losing, and hence BOLD-responses in the ventral

striatum should not differ between the absolute magnitudes of different rewards. In contrast to this notion, a number of studies reported reward magnitude dependent hemodynamic responses in the ventral striatum (e.g. Rolls et al., 2008; Yacubian et al., 2006), whereas others showed magnitude independent differences between favorable and unfavorable outcomes (e.g. Delgado et al., 2003, Elliott, 2003; Bunzeck et al., 2010). One plausible explanation for the discrepancy between results could be that task specific differences impede "gain-adaptation". Alternatively, depending on the experimental task, the BOLD signal itself may be driven by different sources of neuronal activity.

Current standard of knowledge is that the BOLD signal is most strongly related to synaptic current; therefore, it may reflect afferent input to neuron populations and/or local intrinsic processing (e.g. Logothetis et al., 2001; Viswanathan and Freeman, 2007). Looking at the ventral striatum, BOLD-responses are suggested to arise from stimulation of postsynaptic D1 receptors through dopamine release as inferred from a pharmacological MRI study (Knutson and Gibbs, 2007). Significantly correlating BOLD-responses between the ventral tegmental area and the ventral striatum in response to reward prediction errors (D'Ardenne et al., 2008) and dopamine release in both structures (Schott et al., 2008) corroborate the idea of dopaminergic midbrain-driven BOLD-responses in the ventral striatum. Furthermore, at the level of single-unit activity reward prediction errors are generally not seen in the ventral striatum (Niv and Schoenbaum, 2008), thus arguing against intrinsically driven BOLD-responses. Nonetheless, a proportion of neurons in the ventral striatum signal the value of rewards and cues that predict reward (Niv and Schoenbaum, 2008). Congruently, in some neuroimaging studies the BOLD signal in the ventral striatum correlates with reward magnitude (Tanaka et al., 2004, McClure et al., 2004) and not reward magnitude dependent prediction errors. Thus, the BOLD signal in the ventral striatum might reflect cortical input or intrinsic activity if reward absolute reward magnitudes are correlated, whereas it might reflect dopaminergic input if reward prediction errors are related to hemodynamic responses (Daw and Doya, 2006).

In the present study we aimed to explore, whether reward and omission of reward of subjectively different magnitude modulates BOLD-responses in the ventral striatum. If BOLD-responses are scaled to the magnitude of rewards, we speculate that other than dopaminergic midbrain input may modulate the BOLD signal. To further test this

hypothesis we use psychophysiological interaction analysis to derive the neuronal sources of such putative variations.

5.3.3 Results

Voxel-wise analysis

We conducted a whole brain analysis that examined significant activity in the ventral striatum for the four conditions of interest ($AnR_{1, 2, 3}$ $AR_{1, 2, 3}$ $OwR_{1, 2, 3}$ $OnwR_{1, 2, 3}$); we then compared these results to the analogue conditions, in which participants played for no rewards (AnR_n, AR_n, OwR_n, $OnwR_n$). See Table 1 for a description of contrasts and conditions.

Table 1. Contrasts of the first level analysis, testing for activity in the ventral striatum.

Contrasts	
$[AnR_1, AnR_2, AnR_3] > AnR_n$	
$[AR_1, AR_2, AR_3] > AR_n$	
$[OwR_1, OwR_2, OwR_3] > OwR_n$	
$[OnwR_1, OnwR_2, OnwR_3] < OnwR_n$	
Description	
An:	Announcement
A:	Anticipation phase
Ow:	Outcome phase (won trials)
Onw:	Outcome phase (not won trials)
R_x:	Reward magnitude (1 = high, 2 = intermediate, 3 = low)
R_n:	no Reward

Significantly more ventral striatal activity was found in the anticipation phase when playing for rewards compared to no rewards with clear bilateral activation (MNI: -10, 16, -6, $t = 5.77$, $p < 0.001$; MNI: 10, 10, -10, $t = 7.33$, $p < 0.001$, complete list of clusters: Table 2). There was no significant difference in ventral striatal activity

between rewards and no rewards during the won outcome phases. Similarly, no significant differences were found in response to the announcement of differently rewarded trials. However, activity in the ventral striatum was significantly smaller when participants did not win a potential reward compared to not winning in a no-reward control trial (bilateral NAcc, (MNI: -8, 12, -10, t = 5.52, p< 0.001; MNI: 14, 12, -10, t = 4.56, 0.001, complete list of clusters: Table 3).

Table 2. Group maximum t-values and MNI coordinates of fMRI activity during the anticipation $[AR_1, AR_2, AR_3] > AnR_n$ (p < 0.001 uncorrected, cluster size > 30 voxels).

Region	Right/ Left	Cluster Size (Voxels)	Coordinates X	Y	Z	*t*-value	*p* <
Brainstem	R	3911	12	-26	-10	7.46	0.001
Pallidum	L		-14	-6	-6	5.34	0.001
Caudate	L		-8	4	0	5.60	0.001
Accumbens	**L**		**-10**	**16**	**-6**	**5.77**	**0.001**
Accumbens	**R**		**10**	**10**	**-10**	**7.33**	**0.001**
Caudate	R		10	4	2	6.63	0.001
Superior frontal gyrus	R	1070	24	-8	56	7.32	0.001
Thalamus	R	120	18	-22	12	7.16	0.001
Lateral occipital cortex, superior division	L	924	-12	-66	62	4.62	0.001
Middle frontal gyrus	L	1282	-28	-4	48	6.72	0.001
Supramarginal gyrus	L	153	-46	-34	36	6.37	0.001
Superior parietal lobule	R	861	22	-56	56	6.30	0.001
Postcentral gyrus	R	216	32	-34	46	6.05	0.001
Frontal pole	R	114	46	44	24	5.73	0.001
Lateral occipital cortex, inferior division	R	463	42	-66	-2	5.56	0.001
Frontal pole	R	146	34	52	10	5.34	0.001
Lateral occipital cortex, superior division	L	87	-32	-70	14	5.09	0.001

Table 3: Group maximum t-values and MNI coordinates of fMRI "deactivation" after the omission of rewards *[OnwR1, OnwR2, OnwR3] < OnwRn* ($p < 0.001$ uncorrected, cluster size > 30 voxels).

Region	Right/ Left	Cluster Size (Voxels)	Coordinates X	Y	Z	*t*-value	*p* <
Superior frontal gyrus	L	214	-20	22	60	5.73	0.001
Accumbens	**L**	**92**	**-8**	**12**	**-10**	**5.52**	**0.001**
Accumbens, Putamen	**R**	**33**	**14**	**12**	**-10**	**4.56**	**0.001**

Region of interest analysis

Anticipation phase

Analysis of individual FIR time-courses during the anticipation phase (Fig. 1, A) (duration 10 - 12s) extracted from the bilateral NAcc ROI yielded a significant interaction of condition (3) x epoch (10), ($F (3.9, 47.4) = 2.636$, $p < 0.0046$), indicating that certain conditions differed significantly over time. Post hoc paired t-tests at the time-point of the highest peak of the signal (12.5s) revealed significant differences between R_1 (high reward magnitude) and R_3 (low reward magnitude) ($t (df=12) = 4.228$, $p< 0.001$), and a strong trend for differences between R_1 and R_2 (intermediate reward magnitude) ($t (df=12) = 1.759$, $p<0.0502$).

Outcome won

No significant activity within the ventral striatum was found for the outcome phase of rewarding won trials (Fig. 1, B) when compared to non-rewarding won trials in the whole brain analysis. Nevertheless, a repeated measure ANOVA revealed a significant main effect of the factor epoch (10), ($F (2.456, 24.563) = 9.066$, $p< 0.001$) but no significant interaction between condition (3) and epoch (10); thus, indicating that the signal time courses changed significantly over time without differing between conditions. A post hoc single sample t-test at the peak of the mean of all signal time courses indicated a significant increase in signal change ($t (df=10) = 3.404$, $p<0.007$)). The FIR time course of the won, although not rewarded, trials indicated a strong trend in differing at the onset of the outcome phase and differed significantly, that is, 2.5s

thereafter from the time courses of mean of all rewarded conditions (0s=(t (df=10) = 2.457, p<0.034), 2.5s=(t (df=10) = 3.106, p<0.01). This indicates that the hemodynamic response started in not rewarded trials at lower levels, compared to rewarded trials.

Outcome not won

The analysis of individual FIR time-courses during the outcome phase of not won trials (Fig. 1, C) (duration 3s) extracted from the bilateral NAcc ROI, yielded a significant interaction of condition (3) x epoch (10), (F (4.815, 67.411) = 3.2, p < 0.013); therefore, indicating that particular conditions differed significantly over time. Post-hoc paired t-tests at the time-point of the most negative signal change (R_1 = 10 s, R_2 = 7.5 s, R_3 = 10 s) revealed significant differences between R_1 and R_3 (t (df=14) = 4.006, p < 0.001), as well as a trend for significant differences between R_2 and R_3 (t (df=14) = 2.383, p < 0.032). No significant difference was observed between R_1 and R_2 (t (df=14)= 1.521, p < 0.150).

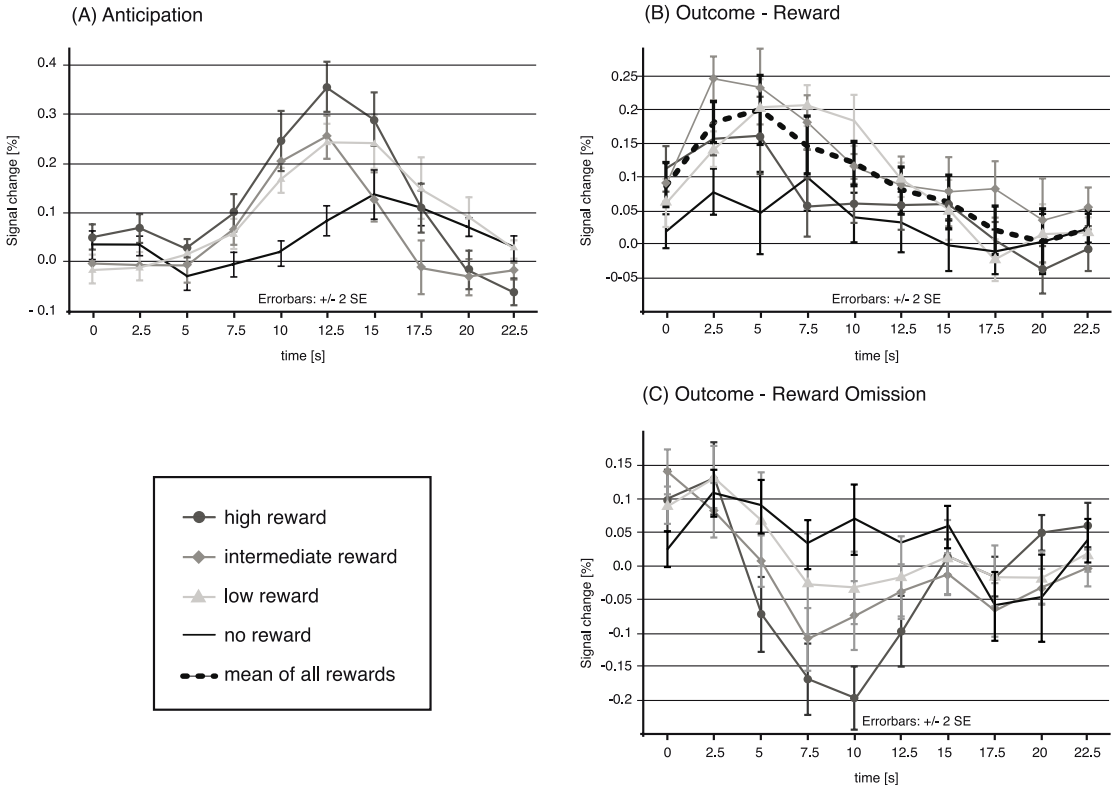

Figure 1. *Event-related hemodynamic responses to different reward magnitudes*. ***A***, Hemodynamic responses during the anticipation phase are modulated by reward magnitude. ***B***, Hemodynamic responses after rewarded outcomes are not influenced by reward magnitude. Averaged time-courses of all rewarded trials (dashed line)

exhibit significant differences to non-rewarded trials. ***C***, After reward omission, signal time-courses significantly decrease in a reward magnitude-dependent fashion. (Note the different scalings in A,B and C).

PPI of reward magnitude and the NAcc after not won outcomes

We discovered that neural responses in the dorsal raphe nucleus (dRN), rostral cingulate zone (RCZ), in the right lateral orbitofrontal cortex (lOFC) covaried more negatively with neural activity in the NAcc as a function of the magnitude of omitted rewards (Table 4). The precise localization of dRN activation is difficult to ascertain with standard MRI techniques. However, previous imaging studies have identified the dorsal raphe nucleus within close range to the cluster in the brainstem, which was found in our study (Lanzenberger et al., 2009; Tanaka et al., 2004). A repeated measures ANOVA ($p < 0.05$) with factors preference levels (3) x cluster location (3) was performed using the mean of the estimated beta weights; it revealed a significant main effect for the factor preference levels ($F (101.7, 1.67) = 5.69$, $p = 0.007$). Post-hoc paired t-tests of the beta estimates in the dRN indicated a trend for significant differences between R_1 and R_2 ($t (df=61) = 2.144$, $p < 0.036$) and R_1 and R_3 ($t (df=61) = 2.802$, $p< 0.0035$). With regard to the beta estimates of the lOFC cluster, post-hoc paired t-tests revealed a trend for significant differences between R_1 and R_2 ($t (df=61) = 1.9962$, $p < 0.051$) and R_1 and R_3 ($t (df=61) = 3.038$, $p < 0.004$,). Mean beta estimates of the RCZ cluster showed a trend for significant differences between conditions R_1 and R_3 ($t (df=61) = 2.184$, $p < 0.033$) and significant differences between R_2 and R_3 ($t (df=61) =3.401$, $p < 0.002$) (Fig. 2).

Table 4. Brain areas showing significant negative changes in connectivity at p < 0.001 uncorrected, cluster size > 30 voxels, except for the Dorsal raphe nucleus (cluster size > 10).

Region (Negative PPI)	Right/ Left	Cluster Size (Voxels)	Coordinates			*t*-value	*p* <
			X	Y	Z		
Rostral cingulate zone	**-**	**545**	**0**	**34**	**12**	**7.39**	**0.001**
Lateral orbitofrontal cortex	**R**	**341**	**34**	**28**	**-22**	**6.06**	**0.001**
Dorsal raphe nucleus	**L**	**16**	**-2**	**-32**	**-16**	**3.73**	**0.001**

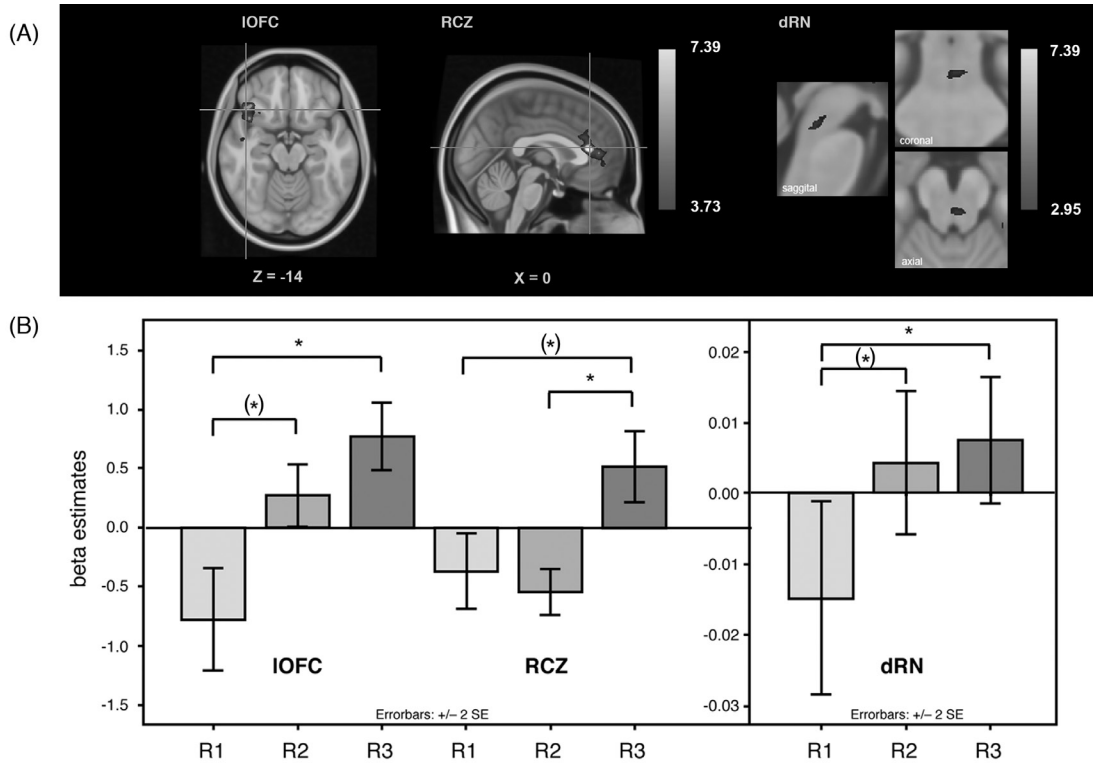

Figure 2. *PPI results*. ***A***, Brain structures significantly changing co-activity with NAcc as an inverse function of reward magnitude (voxel height threshold: p < 0.001, voxel extent threshold, p < 0.05 family-wise error (FWE) corrected, lOFC, lateral orbitofrontal cortex, RCZ, rostral cingulate zone, dRN, dorsal Raphe nucleus (cluster extent threshold > 10 voxel)). ***B***, Mean beta estimates of the NAcc ROI - PPI regressors. Positive values indicate positively correlating co-activity, whereas

negative values indicate negatively correlating co-activity. Asterisks indicate significant differences * ($p < 0.05$, one-sided, corrected for multiple comparisons). A trend for a significant difference is indicated by asterisks within brackets (*) ($p < 0.05$, one sided, uncorrected for multiple comparisons).

5.3.4 Discussion

The goal of this study was to examine whether BOLD-responses in the ventral striatum might be mainly driven by RPE-related neuronal activity in the dopaminergic midbrain or neuronal activity, related to absolute magnitude coding. We used individual ratings of rewards and associated these to Nucleus Accumbens (NAcc) activity to assure that rewards truly differ in the subjectively perceived magnitude. Our analysis focused on the NAcc, since this part of the ventral striatum was most consistently activated across experimental conditions. Furthermore, we employed a NAcc probability map, in order to circumvent the problem of non-independence between analysis levels.

Amplitudes of BOLD-responses in the NAcc reflected the expected reward magnitude while subjects were anticipating rewards. This is in line with previous studies, indicating magnitude dependent reward prediction error signals in the dopaminergic midbrain (e.g. Tobler et al., 2005) and ventral striatum (e.g. Knutson et al., 2001, Delgado et al., 2003). The same area exhibited BOLD-responses during reward delivery and was unaffected by reward magnitude; thus, supporting the previously reported effect of reward prediction error "gain adaptation" (Tobler et al., 2005, Bunzeck et al., 2010). We further identified significant negative deviations in BOLD-responses in the NAcc after the omission of rewards. Interestingly, this decrease in BOLD-responses was found to be magnitude-dependent. This finding argues in favor of reward magnitude coding at an absolute scale for the case of reward omission. A psychophysiological interaction analysis implies that the differences in BOLD-responses, related to the magnitude of omissions are predominantly driven by other structures than the dopaminergic midbrain.

Reward anticipation

During the anticipation phase, there was a clear difference in hemodynamic responses in trials in which rewards could be anticipated compared with control trials without reward. Furthermore, at the peak of the signal change curve (12.5 s after spinning wheel onset) significant differences were evident between large and intermediate reward magnitude and large and small reward magnitude, but not between intermediate and small reward magnitude. Thus, this finding of reward magnitude-dependent activity in the ventral striatum during anticipation is consistent with previous imaging studies (Breiter et al., 2001; Galvan et al., 2005; Knutson et al., 2001a) reporting a general albeit not necessarily linear dependence of reward magnitude and ventral striatal activity. It is noteworthy that the observed effect of anticipatory reward magnitude coding may be conceptualized as a magnitude dependent reward prediction error signal. Since subjects did not know the exact moment of the beginning of a trial (random inter-trial-interval), the presentation of the reward-predicting cue reflects a prediction error, which is scaled to the magnitude of the probable forthcoming reward. The observed response pattern complies with reward prediction error-dependent dopaminergic midbrain-spiking patterns evidenced in non-human primates during the anticipation of different rewards (Tobler et al., 2005; Bayer and Glimcher, 2005). This suggests strong dopaminergic innervation of the ventral striatum.

A substantial difference between Tobler et al.'s (2005) study and our study was the longer delay between reward predicting stimulus and reward (11.5 – 16 s in our study compared to approximately 2 s in Tobler's study). We initially expected hemodynamic responses to the onset of the announcement of the reward. However, our analysis did not indicate significant responses to this reward-predicting stimulus. This lack of finding may be due to decreases in dopaminergic response in relation to expected longer delays of rewards as reported by Kobayashi and Schultz (2008). Nevertheless, as dopamine responses have been frequently observed to generalize to stimuli resembling reward predictors (Ljungberg et al., 1991; Schultz and Romo, 1990) the late peaking hemodynamic response in the ventral striatum could reflect a later reward-predicting cue. This cue might be the slowing of the wheel of fortune; it likely represents a more salient and temporally closer predictor for future reward. Future studies will be necessary to better understand the influence of different delays

between cues and rewards on the signal time course of hemodynamic signals in the ventral striatum, as well as spike signaling of dopaminergic neurons.

Outcome won

The analysis of event-related FIR time-courses of rewarded outcome trials indicates a significant signal change in the NAcc with a BOLD-response characteristic that could possibly reflect activity in relation to the processing of positive RPE's. Unlike the reward magnitude-dependent responses in the ventral striatum during anticipation, the FIR time-courses did not differ between absolute reward magnitudes after rewarded outcomes. The fact that signal time courses gradually increased irrespective of reward magnitude lends support to the previously reported effect of "gain-adaptation" of RPEs (Tobler et al., 2005, Bunzeck et al., 2010). In these two studies, subjects (humans and non-human primates) were presented three cues predicting pairs of rewards of different magnitude. They could nicely demonstrate that the pattern of prediction errors is adaptively scaled with respect to the possible alternatives. In other words, winning vs. not winning a reward always elicits the same neuronal response, independently of the absolute magnitude. In contrast, in our study, to play for a reward of specific magnitude always meant that this reward could be won or not won. Similarly as in the studies of Tobler et al. (2005) and Bunzeck et al. (2010) the range of outcomes was known. Thus, a positive RPE (e.g. winning) may normalize to the absolute difference between two outcomes (e.g. gain of a large reward vs. omission of a large reward), thereby resulting in a magnitude-indifferent increase in hemodynamic response. However, deducing this interpretation from the non-finding of differences is obviously problematic from a statistical point of view.

Regarding previous research, a number of studies did find reward magnitude dependent hemodynamic responses in the ventral striatum (Rolls et al., 2008; Yacubian et al., 2006). Other studies showed magnitude *in*dependent differences between favorable and unfavorable outcomes (e.g. Delgado et al., 2003, Elliott et al., 2003; Bunzeck et al., 2010). The discrepancy between the results might be explained by differences in the experimental tasks. For instance, in the study of Rolls et al., (2008) and Yacubian et al., (2006) subjects could choose between alternatives with different reward magnitude in combination with different reward probabilities. The outcome was always probabilistic and hence the needed knowledge about alternative

outcomes for reward prediction gain adaptation was possibly not met. In contrast, in the studies of Delgado et al., 2003, Elliott et al., 2003 and Bunzeck et al., 2010 only two known alternative outcomes per trial were possible, thus RPE-gain adaptation was possibly feasible. In addition, lending further support to our interpretation, there exists general agreement that the human reward system largely encodes reward values in relation to possible outcomes and not on an absolute scale (De Martino et al., 2009; Elliott et al., 2008; Fujiwara et al., 2009; Nieuwenhuis et al., 2005).

Outcome not won

Our findings reveal that hemodynamic responses upon reward omission gradually decrease in relation to the reward magnitude. This is in contrast to the hypothesis of gain-adaptation, which also applies to negative prediction errors, as shown in midbrain dopamergic firing rates which were also scaled to the difference between alternative outcomes and thus did not differentiate between the absolute magnitudes of outcomes (Tobler et al., 2005). In light of this and the finding of magnitude independent BOLD-responses after gaining rewards, our result of a reward magnitude-dependent decrease in BOLD-response was surprising. However, alternatively to spike-frequency reward prediction error magnitude coding in the dopaminergic midbrain, which is anyway limited in the case of spiking depression in response to negative prediction errors, RPE-magnitude-dependent graded responses in dopaminergic midbrain neurons have been reported in terms of the *duration* of the below base-rate spiking depression (Bayer et al., 2007). This may have affected BOLD-responses in synaptic target regions, such as, the NAcc. However, it is not yet clear how longer suppression influences the amplitude of negative hemodynamic responses.

Compared to the hemodynamic response after won outcomes the negative BOLD response peaked 2.5-5 s later. The physiological meaning of the latency of BOLD-responses is only scarcely investigated but it has been conjectured that prolonged neuronal activity would produce both larger and relatively delayed peaking of the BOLD response (Henson et. al., 2002). Adopting this idea to later peaking *negative* BOLD-responses could indicate that reward omissions elicit longer deactivations in the ventral striatum after reward omissions, compared to activation due to gains. However, to our knowledge, latency effects of negative hemodynamic responses have

not yet been investigated and it is therefore impossible to draw conclusions on this difference.

Rather than the dopaminergic system, it may be the serotonergic system (e.g., the dorsal raphe nucleus (dRN)) that sends strong projections to the ventral striatum (Azmitia and Segal, 1978) and influences the encoding of negative RPE; thereby, affecting the graded decrease in hemodynamic signal in the NAcc. However, evidence that phasic serotonergic signaling drives negative RPEs has only been deduced from computational models (Daw et al., 2002) so far and has yet to be proven physiologically.

Psychophysiological interaction analysis (PPI)

In order to explore which structures modulate the graded negative responses in the NAcc, we performed a psychophysiological interaction analysis (PPI) isolating those structures that change their functional connectivity to the NAcc as an inverse function of reward magnitude in reward omission trials. The analysis revealed, that activity in the brainstem, possibly the dorsal Raphe nucleus (dRN), rostral cingulate zone (RCZ), and in the right lateral orbitofrontal cortex (OFC) covaries with neural activity in the NAcc as the magnitude of the omitted reward increases.

Experiments conducted with monkeys have suggested a strong interaction between the dopaminergic and serotonergic system. For example, it has been shown that the serotonin system, which originates in the dRN, inhibits dopaminergic function in the midbrain (Dray and Straughan, 1976; Trent and Tepper, 1991), as well as at the terminal dopaminergic fields, namely, the NAcc and striatum (Kapur and Remington, 1996). Further evidence for a mechanism, which subserves serotonin's inhibitory effect on dopamine, comes from an electrophysiological study by Jones and Kauer (1999), demonstrating that the excitatory glutamatergic synaptic transmission onto VTA neurons is depressed through the activation of serotonin receptors. This is in contrast to the interaction between dRN activity and dopamine, and suggests their involvement in the processing of negative prediction errors. Recent studies have revealed that dRN neurons respond to expected and received rewards (Nakamura et al., 2008; Lanzenberger et al., 2009), as well as to the evaluation of delayed rewards (Tanaka et al., 2004). In view of this, we can only conjecture that the dRN “down-

regulates" (probably through serotonergic input) activity in the NAcc, which may account for the graded decreases in hemodynamic responses.

An important role in monitoring the rewarding features of stimuli is attributed to the OFC because of its extensive multisensory connections (Padoa-Schioppa and Assad, 2006; Walton et al., 2004). More specifically, the lateral OFC receives input from visual areas (Ongur and Price, 2000), and it is active during evaluation of punishing stimuli (Kringelbach and Rolls, 2004; Seymour et al., 2005). Prominent projections from the lateral OFC to the NAcc (Haber et al., 1995) provide further support for the concept of a modulating impact produced by the lateral OFC on the NAcc. We suggest that after receiving sensory information about a punishing event, the lateral OFC evaluates this information in terms of its rewarding value and subsequently down-regulates activity in the NAcc and dopaminergic midbrain structures.

The RCZ is often co-active with the lateral OFC during evaluation of negatively valued events (Kringelbach, 2005). As shown in non-human primates, these two structures maintain strong anatomical interconnections (Ongur and Price, 2000), suggesting that they operate as a linked pair (Kringelbach and Rolls, 2003). The RCZ also receives projections from limbic structures, such as, the ventral striatum (Kunishio and Haber, 1994) and amygdala (Barbas and De Olmos, 1990); it generally represents a main target area of the mesocortical dopamine system, which originates in the ventral tegmental area (Gaspar et al., 1989). It has been previously suggested that pyramidal cells in the RCZ are disinhibited by phasic decreases of mesencephalic dopaminergic inputs, which result in error related negativity (ERN), that is a negative deflection in the ongoing electroencephalogram (EEG) emerging when humans evaluate events, which are inconsistent with their expectations (Holroyd and Coles, 2002). In line with this theory, Münte et al., (2007) conducted a study employing simultaneous intraoperative recordings and EEG in an awake human patient. These researchers found decreases in the local field potential within the NAcc, which were highly correlated to the ERN signal in the EEG recordings. Furthermore, they showed that the error-related activity in the NAcc precedes the ERN by 40 ms; thus, suggesting a directional influence of the NAcc to the RCZ. In our experiment, if a highly preferred reward was not obtained, then it represented a more relevant violation of what had been expected, in contrast with the omission of a less preferred reward. Neurons in the RCZ may process this violation and trigger the subsequent (re)formation of future expectations, this resulting in an outcome-based optimization

of forthcoming behavior. In our study, the participants had no means of influencing the outcome of the wheel of fortune game; therefore, they were unable to optimize future behavior. Nevertheless, this basal learning mechanism may be triggered irrespective of whether future behavior can be optimized on the basis of outcome.

In conclusion, ventral striatal BOLD-responses during anticipation and after gain of different rewards exhibit response patterns of RPE's as shown before (Tobler et al., 2005; Bunzeck et al., 2010, Delgado et al., 2003). Thus, in these phases, the BOLD signal in the ventral striatum likely reflects predominantly ennervation of activity of the dopaminergic midbrain. In contrast to dopaminergic midbrain responses to the omission of rewards, hemodynamic responses were scaled to the absolute reward magnitude, suggesting that activity in the NAcc may be modulated through inputs of other than dopaminergic midbrain neurons. The PPI analysis used in our study has revealed that activity in the dRN, lateral OFC, and RCZ was negatively related to BOLD-deactivations in the NAcc in association with the omission of rewards of different magnitude. We suggest that the dRN and lateral OFC have a graded inhibitory effect on NAcc after reward omission whereas RCZ is disinhibited by the deactivation of neural activity in the NAcc. Intracranial recordings could possibly yield evidence for this proposal.

5.3.5 Experimental Procedure

Participants

Sixteen healthy adult voluntary participants (9 female and 7 male, mean age of 24 ± 4) were recruited from the University of Zurich and ETH Zurich, Switzerland. In contrast to previous studies, we manipulated reward magnitude on a subjective, individual scale; this required the selection of participants based on specific criteria. In our previous studies (Koeneke et al., 2008), we were able to show (1) that – within a certain product category, e.g., chocolate bars or sneakers – different brands can be arranged in a preference hierarchy for each individual and (2) that this individual brand preference hierarchy is reflected in the pattern of brain activity during a gambling paradigm. Neural structures whose activity was modulated by individual brand preferences were similar to structures identified in previous studies that manipulated the reward according to an objectively quantifiable scale, for example,

monetary rewards. The aspect of modulating reward values through brand preferences will be published elsewhere.

Similar to our previous work, we used different product brands to represent various reward magnitudes in the present study. Determining the individual brand hierarchies required a detailed assessment of brand preferences embedded in a two-stage selection procedure. During the first stage, a paper and pencil questionnaire was distributed to students in different courses of the Psychology Department of the University of Zurich. Two-hundred students completed the questionnaire, from which 50 respondents indicated that they (a) wore sneakers at least from time to time, (b) cared about sneakers, (c) cared about brands when it came to sneakers, and (d) expressed differentiated brand preferences in a constant sum point allocation "chip game" between different sneaker brands. These 50 respondents were invited to the second round. Twenty-seven of the pre-selected participants accepted the invitation and filled out a second, computer-based questionnaire that aimed to measure individual brand preferences in more detail with a choice-based procedure (the GfK Price Challenger, GPC, Wildner, 2003), and another constant sum chip game. Of those, 18 respondents were invited to our fMRI study. These participants expressed preferences that were consistent across the two measures and widely dispersed, in order to allow for clear brand differentiation. Two participants dropped out due to personal reasons. Based on the preference data gathered in the second stage of the selection procedure, three sneaker brands were determined for each subject: (1) her/his favorite brand (high reward: R_1), (2) her/his least preferred yet still acceptable brand (low reward: R_3), as well as (3) one intermediate brand (intermediate reward: R_2) that ranked between the top and the bottom brand. Hence, reward magnitude in the present study had three parameter values.

The local ethics committee approved our study and the research participants gave written informed consent. The tasks and testing procedures were in accordance with institutional guidelines and the study conformed to the Declaration of Helsinki. Participation was compensated with 50.00 CHF, and if during the experiment a pair of sneakers was won, then research participants received a voucher worth 150 CHF.

Design and Procedure

Participants played a virtual wheel-of-fortune game projected onto a translucent screen that could be viewed inside the scanner via a mirror. The experiment consisted of four runs with 25 trials each. Individual T1-weighted anatomic brain images were recorded after the actual experimental sessions. The total scanning time was approximately 50 minutes. Before being scanned, participants were briefly informed about MRI / fMRI methodology; then each participant was instructed to (1) complete a questionnaire that tested for individual MR-suitability and (2) to give his / her informed consent. Next, participants were requested to read a short instruction manual, which explained the procedures of the experiment. Participants then completed two test trials of the wheel-of-fortune game outside the scanner, in order to assure that they had understood the task correctly. The overall prize that could be won in our experiment was a voucher (worth 150 CHF) for a particular brand of sneakers. The subjects played for this voucher in a lottery, which took place after the scanning session. During the scanning session, the subjects were able to win lottery tickets that increased their chances of winning in the subsequent lottery. In other words, a won trial in the wheel-of-fortune game increased the probability of winning the voucher for a certain brand of sneakers.

In each wheel-of-fortune trial, one out of 25 lottery tickets per brands could be won (i.e., 75 lottery tickets in total). Trials were brand-specific, meaning that a won trial increased the chances of winning a voucher for one specific brand (R_1, R_2 or R_3), which was announced at the beginning of the trial. During the scanning session, the number of won lottery tickets for each brand was displayed. After the scanning session, the subjects were presented with three pots (one for each brand) that each contained 25 lottery tickets, with one lottery ticket being the joker. The subjects then drew the amount of won lottery tickets separately for each brand. If the joker was drawn, participants received the voucher for the particular brand. If more than one voucher was won, they could freely choose one to take home. The chance to win was pseudo-randomly varied at a chance of 50 percent. Thus, participants had the cumulative chance to win one of the three vouchers of 87.5 percent. The sequence of the brands the participants played for were pseudo-randomly distributed, to ensure enough trials of every possible combination (brand, outcome) for the analysis. In addition, 25 trials in which no lottery tickets could be won were randomly

interspersed in the experiment, in order to detect brain areas responding to the wheel-of-fortune game itself; this resulted in a total of 100 trials.

A trial consisted of a brand announcement phase (0.5 –2 s), a response phase (choice between green or red; 1-2 s), a prospect phase (wheel of fortune spins; 10-12 s), an outcome phase (outcome is presented; 3s), a blank screen with a fixation cross (4-5 s), a picture of the actual balance (2 s), and a blank screen with a fixation cross (6 s) (Fig. 3). During the announcement phase, the logo of the brand that subjects were playing for in the current trial was presented in the center of a wheel-of-fortune that consisted of twelve colored (6 green and 6 red) fields. During the response phase, participants could choose one color by pressing a button. The button-to-color assignment was kept constant across the trials. The chosen color field remained visible underneath the wheel while the other color field disappeared so that participants did not have to memorize their choice. The anticipation phase started with the wheel-of-fortune rotating and slowing down to a halt after 10-12 s. The wheel-of-fortune slowed down asymptotically, to simulate a realistic roulette-like game. The ensuing outcome-phase started after the wheel had stopped. The outcome achieved was indicated by a field that came to a halt under a pin at the top of the wheel, as well as by a text box (i.e., "You have won 1 lot / You have not won"). During the outcome-phase the logo at stake was still visible. A trial was won when the color chosen by the subject was consistent with the color of the field that came to a halt under the pin. To avoid participants memorizing account balances, the balance of the number of lottery tickets for the respective brand, which had been acquired thus far, was indicated in each trial. This number was also translated into the probability of winning a voucher and was represented as a bar chart. A blank screen with a fixation cross was presented for 6 s before the next trial started, in order to ensure that the fMRI signal could level back to a task-unspecific baseline.

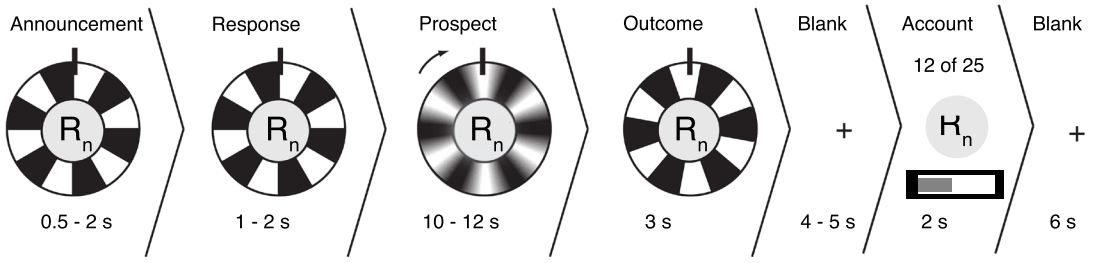

Figure 3. Experimental design of the wheel-of-fortune game.

fMRI acquisition

A Philips Intera 3T whole-body MR unit (Philips Medical Systems, Best, The Netherlands), equipped with an eight-channel Philips SENSE head coil was used, to acquire magnetic resonance images. Anatomical images of the whole brain were obtained by using a T1-weighted three-dimensional, spoiled, gradient echo pulse sequence (repetition time (TR)=20 ms, echo time (TE)=2.30 ms, flip angle 20°, field of view (FOV)=220 mm, acquisition matrix=224 x 224, voxel size=1 mm x 1 mm 0.75 mm, 180 slices, slice thickness=0.75 mm). Functional data for the behavioral tasks were obtained from 280 whole-head scans per run using a Sensitivity Encoded (SENSE) (Pruessmann et al., 1999) single-shot echoplanar imaging technique (TR = 2500ms, TE = 35ms, flip angle = 78°, FOV = 220mm, acquisition matrix= 80 x 80, 33 transverse slices, voxel size= 1.72 mm x 1.72 mm x 4 mm).

Data Analysis

Preprocessing

Artifact elimination and MRI data analysis were performed using MATLAB 2006b (Mathworks Inc., Natick, Massachusetts, USA), and the SPM5 software package (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/software/spm5). The first three images were discarded, to allow for steady-state magnetization. All images were realigned to the first image of the first run, slice time corrected and spatially normalized into standard stereotactic MNI space (EPI template provided by the Montreal Neurological Institute), interpolated to a voxel size of 2 x 2 x 2 mm and spatially smoothed using a 8-mm full-with-at-half-maximum Gaussian kernel.

Voxel-wise analysis

Whole brain analysis was performed using a general linear model as implemented in SPM5. The design matrix included regressors modeling the onsets and durations of the announcement phase, response phase, anticipation phase, the two possible types of outcome (won/ not won) and the actual balance. Separate regressors were introduced

for each preference level and the non-rewarding condition in the announcement phase, the anticipation phase, and the two outcome phases. The announcement, response and anticipation phases, as well as the blank screen between the outcome and balance varied in duration. Also, the time lag between motor response that occurred when choosing a color and at the onset of the anticipation phase (the start of the spinning of the wheel-of-fortune) was temporally jittered. This was implemented, since our aim was to temporally de-correlate two ensuing regressors and avoid inflation of variance; thereby, increasing model-sensitivity. The resulting regressors were convolved with SPM's canonical difference of gamma hemodynamic response function. After high-pass filtering (cut-off of 128 s), an individual statistical model was computed for each participant.

The goal of the whole-brain analysis was to assure significant activity in the ventral striatum, in order to further analyze region-specific hemodynamic signal time courses. Thus, contrasts were calculated for the announcement, the anticipation phases, between R_1, R_2, R_3 and the non-rewarding (R_n) trials, for the two outcomes (won/not won) R_1, R_2, R_3 and the non-rewarding trials (R_n) (Table 1). To allow for a population level inference, the maps of contrast coefficients, which were controlled for random effects, were collectively submitted to one-sample t-tests against the null hypothesis of no activation.

Regions of interest analysis

Region of interest (ROI) analyses were performed using MARSBAR, the ROI toolbox for SPM; version 0.41 (http://marsbar.sourceforge.net/), and SPSS (Rel. 16.0, SPSS). Since the NAcc (bilaterally) was found to be consistently activated within the ventral striatum, we chose the bilateral NAcc of the Harvard-Oxford subcortical probabilistic atlas, provided by the FSL Software Library (Analysis Group, FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html). We made this choice, instead of defining our ROI from activation patterns, because the former involves a risk that may have resulted in non-independence between test hierarchies. A finite impulse response (FIR) model was employed since we intended to extract event-related time courses of each experimental condition (10 time bins of 2.5 s); thereby, calculating the best estimate of the fMRI signal for each scan after adjusting for other effects of the model.

The analysis targeted preference-dependent FIR signal time courses of the anticipation phase (A), the outcome phase of won trials (OW), and the outcome phase of not won trials (OnW). The resulting FIR-time courses, which were time-locked to the onsets of the three phases were analyzed by using a repeated-measures ANOVA ($p < 0.05$) with the within-subject factors: preference-level (n=3) and epoch (n=10). If one single FIR values was above or below 3 * interquartile range, then FIR signal time courses of those subjects were excluded from the analysis. Average signal changes were compared across condition types at the time of positive or negative peaks (depending on the overall time-course) by using paired t – tests. Unless otherwise indicated, significance thresholds were set at $p < 0.05$ and Bonferroni-corrected for the number of paired t-tests.

Psychophysiological interaction analysis (PPI)

A psychophysiological interaction means that the connectivity of one area to another changes significantly in relation to an experimental variable (Friston et al., 1997). However, it should be kept in mind that PPI analyses do not inform us about causality. In our study, we aimed to reveal which neural structures may have influenced reward-magnitude-specific decreases in neural activity in the NAcc during the outcome phase of not won trials (OnW); subsequently, suggesting the role of inhibitory interactions. In order to accomplish this goal, individual time series were extracted from the bilateral NAcc ROI (which we also used for the standard ROI analyses) by using the first eigentimeseries (principal component). The PPI is defined as the interaction between the NAcc time series and the preference levels introduced as a first order parametric modulation in not won trials. To test for group effects, single-subject first-order parametric modulatory contrasts were subjected to a one-way ANOVA. If clusters demonstrated significant connectivity ($p < 0.001$, voxel extent threshold, $p < 0.05$ family-wise-error (FWE) corrected), then mean beta weights of the clusters of the three different preference levels were extracted and further compared with paired t-tests. Because the dorsal Raphe nucleus (dRN) has been previously suggested to influence the negative prediction error signal in the ventral striatum, the cluster extent threshold was lowered to a cluster size of 10 voxels for the brainstem region surrounding the dRN.

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5.4 Experiment 3: Topographic ERP Analysis of Reward Value- and Valence-Coding

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5.4.1 Summary

Economic theory distinguishes two concepts of utility: decision utility, objectively quantifiable by choices and experienced utility referring to the satisfaction by an obtainment. Up to date, experienced utility is typically measured with subjective ratings. This study intended to quantify experienced utility by global levels of neuronal activity. Neuronal activity was measured by means of electroencephalographic (EEG) responses to gain and omission of graded monetary rewards at the level of the EEG-topography in human subjects. A novel analysis approach allowed approximating psychophysiological value functions for the experienced utility of monetary rewards. In addition, we identified the time-windows of the ERP and the respective intracortical sources, where variations in neuronal activity were significantly related to the value or valence of outcomes. Results indicate that value functions of experienced utility and regret disproportionally increase with monetary value, thus contradict the compressing value functions of decision utility. The temporal pattern of outcome evaluation suggests an initial (~250 ms) coarse evaluation regarding the valence, concurrent with a finer-grained evaluation of the value of gained rewards, whereas the evaluation of the value of omitted rewards emerges later. We hypothesize that this temporal double dissociation is explained by reward prediction errors. Finally a late, yet unreported reward-sensitive ERP-topography (~500 ms) was identified. The sources of these topographical covariations are estimated in the ventromedial prefrontal cortex, the medial frontal gyrus, the anterior and posterior cingulate cortex and the hippocampus/amygdala. The results provide important new evidence regarding „how“, „when“ and „where“ the brain evaluates outcomes with different hedonic impact.

5.4.2 Introduction

To optimize behavior, an organism needs to assess the experienced utility of actions or objects compared to its expected utility. The expected utility of a prospect is behaviorally inferred from revealed choices (Becker et al., 1964). On the other hand, the experienced utility, referring to the hedonic impact of an obtainment (Bentham, 1798) is more difficult to objectively quantify as it represents a transient subjective state of emotion.

Recent research using functional magnetic resonance imaging has identified neuronal structures that are involved in the evaluation of rewarding and punishing outcomes and therefore implicitly provide physiologically-based correlates of experienced utility and experienced regret (Knutson et al., 2003; O'Doherty et al., 2003; D'Ardenne et al., 2008; Coricelli et al., 2007). Electroencephalography (EEG) studies revealed insights to the temporal course of outcome evaluation. Besides others, most prominently two event-related potentials (ERP) have been identified; the feedback error-related negativity (fERN) (Holroyd et al., 2003; Hajcak et al., 2005) and its pendant, the feedback correct-related positivity (fCRP) (Holroyd et al., 2008). The fERN-amplitude increases when outcomes are worse than expected, whereas the fCRP is more pronounced, when outcomes are better than expected. Consequently, the difference between the expectation and outcome is thought to define the experienced utility of the outcome (Yeung et al., 2005; Potts et al., 2006).

Up to the here presented study it has not been investigated how different magnitudes of outcomes are related to the magnitude of global brain activity. From a logical point of view, neuronal activity elicited by stimuli solely differing in reward magnitude must reflect their hedonic impacts. Consequently, the quantification of the magnitude of brain responses of a reasonable sample of different rewards would enable to construct value functions for experienced utility in the case of gain and experienced regret in the case of omission. Value functions for experienced utility and regret may be of profound interest because they could help clarify why people sometimes fail to choose what maximizes their happiness (Hsee and Hastie, 2006).

To derive such value functions, high-density EEG was recorded while subjects played a wheel-of-fortune game, during which they could win graded monetary rewards. In addition, we aimed to extend knowledge on electrophysiological responses to rewards

by circumventing common methodological issues: A majority of previous studies investigated only difference-waveforms between two conditions, like two magnitudes of outcomes. Hence, it is impossible to deduce the source of the variance (Luck, 2005). Another potential drawback of the "classical" ERP approach is that waveforms are observed at a small number of beforehand selected electrodes. These electrodes are not representative for the underlying spatio-temporal distribution of brain activity (Murray et al., 2008). Extending the "classical" ERP approach, we investigated outcome related responses at the ERP-topography using the whole set of electrodes. With topographic EEG measures the full spatial and temporal information of EEG is available and thus can be used to estimate the intracerebral sources of EEG activity. Using this information, we delineated latency and localization of brain activity covarying (and not only differing) with reward value.

5.4.3 Methods

Subjects

Sixteen healthy subjects (10 female, 6 male, mean age: 26.4 years (*SD* = 5.0)) were recruited at the University of Zurich. Subjects reported having no psychiatric conditions. The local ethics review committee approved the study. Subjects signed informed consent documents before the start of the experiment.

Procedure

Subjects were seated in 1 m distance from a computer screen (resolution: 1024 * 768 pixel, screen size: 17'') in a sound, light, and electrically shielded EEG recording room and played a wheel of fortune game (Fig. 1).

On each trial of the experiment three coins were presented to the subjects. The sum of the three coins indicated the monetary reward value at stake. The reward value was

pseudo-randomly assigned, ranging from 10 Swiss centimes to 1 Swiss franc (≈ 0.75 €). To assure visual similarity between the different monetary reward values, always three coins were presented with one or two visually scrambled coins, depending on the monetary value (for an example see Fig. 1).

By pressing one of two buttons, subjects chose a color (green or red) to bet on. Depending on the chosen color, a rectangle surrounding the picture with the coins adapted its color accordingly. 500 ms after the button press a second rectangle, framed by the outer rectangle, started to alternate in coloring from red to green and back. The speed of alternation asymptotically decreased until the inner rectangle stopped after 3500 – 3800 ms. A trial was won, if the inner and outer rectangle matched color, increasing the actual balance of a subject for the amount of money played for. Whenever the color of the inner and outer rectangle was different, the money at stake was omitted. The time point of definite outcome was indicated through a white border of the inner rectangle. The picture indicating the outcome was presented for 1500 ms. The next trial started after the presentation (1000ms) of a blank screen with a fixation cross.

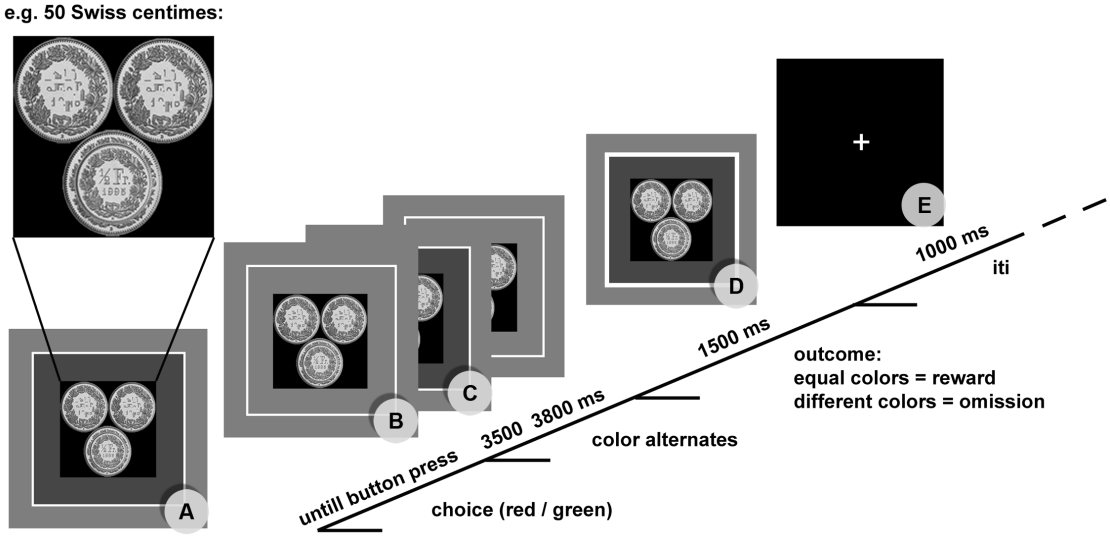

Figure 1. *Course of the experimental paradigm*. A) Reward at stake is presented (e.g. 50 Swiss centimes). B) Subject chooses color via button press. C) The inner rectangle starts alternating and stops after 3500-3800 ms. D) If the chosen color (outer rectangle) and the inner rectangle match, the subject wins. If the two rectangles are of different color, the potential reward is omitted. E) After the presentation of a blank screen for 1 second the next trial starts with a different reward value at stake.

In each of total 300 trials, a real monetary reward was at stake. Each reward value was played for 30 times, with a probability of 50% for gain and omission, resulting in a total monetary gain of 82.50 Swiss francs. Subjects were informed about the probability to win. Because the analysis (outlined below) is sensitive to unbalanced numbers of observations, we chose to pseudo-randomly predefine the sequences of outcomes of trials using randomized arrays obtained at *www.random.org*. Consequently, the 20 experimental conditions (reward value (10) x outcome (2)) were randomly distributed in time. There were 6 blocks of 50 trials for each subject presented in different random order. The subjects were truthfully told, that they could keep the money they won. Since the total gain was equal for all subjects, they were asked before the experiment whether they knew about any other participants and their gain. If a subject indicated to know of another's gain, a different randomization procedure was available resulting in a similar gain (85 Swiss francs). None of the subjects indicated knowing about the monetary gains of others.

EEG data acquisition and preprocessing

Scalp EEG was recorded at 250 Hz with a Geodesics system (Electrical Geodesics, Inc., USA) from 129 scalp electrodes referenced to the vertex. Impedances were maintained at 30 kΩ or less. 21 electrodes located on the outermost circumference (chin and neck) were omitted, because the head model implemented in sLORETA (Pascual-Marqui, 2002), which was used to localize intracerebral sources, does not cover these electrodes. The remaining 109 electrodes were submitted to further analysis. The EEG was filtered offline from 1.5 to 30 Hz. Eye movement artifacts were removed from the data using independent component analysis (ICA). Trials containing further artifacts after visual inspection were excluded from the ERP analysis. EEG data was recomputed against the average reference. Artifact-free EEG epochs of 1200 ms were extracted with onsets 200 ms before the presentation of the outcome stimuli (Fig. 1 d). The average number of artifact-free data epochs from each subject was: 134.4 (of totally 150), SD = 15.2 for the rewarded outcomes and 132.0 (of totally 150), SD = 16.2 for the omitted outcomes. ERP maps of each reward

condition were averaged for each subject, and grand-average ERPs across subjects were computed for each reward condition and across reward conditions.

Definition of the time-window of analysis: Consistent ERP-topography across subjects

To restrain the temporal window of analysis we followed a recently suggested approach (Koenig and Melie-Garcia, 2009, 2010) that detects the time periods in the ERP where similar intracortical generators are active across subjects. Since similar generators imply similar topographies, topographies across subjects are tested for consistency. For this test the Global Field Power (GFP) of the grand mean ERPs is taken as the measure of effect size. The null hypothesis states that for each time point the GFP of the grand mean ERP (i.e. the mean ERP across subjects of the mean ERPs within subjects) may be observed by chance. To test this hypothesis, the GFP of the grand mean ERP was compared to 5000 GFPs of the grand mean ERPs that were constructed by randomly shuffling the measurements across electrodes of the grand mean ERP within each subject. To obtain the probability of the null hypothesis, the percentage of cases was computed where the GFP obtained after randomization was larger than the GFP obtained in the observed data. This procedure was applied for grand means of won outcomes, lost outcomes and all outcomes.

Topographic Analysis of Covariance (TANCOVA)

Topographic analyses of covariance (TANCOVA) was used to identify the time points where the global scalp field potentials significantly covaried with the external variables. This method of analysis introduced by Koenig and colleagues (2008) relies on the fact that ERP fields are additive. Therefore, the existence of a source that is active proportionally to an external variable results in a single topography that is added to the ERP proportionally to the external variable. To retrieve the topography that is proportional to the external variable at a given point in time, the covariance of the external variable with the potentials at each electrode at that point in time is

computed. The obtained covariance map β represents the map corresponding to the generators that activate proportionally to the external variable at the given point in time. Using the GFP of this covariance map as an effect size allows testing time-frame for time-frame for significant covariation by applying randomization statistics as described in Koenig et al. (2008).

For the time-windows indicating significant ($p < 0.01$) consistent scalp topographies across subjects, TANCOVAs were computed for the variables: reward value of gains (levels: 10), reward value of omitted outcomes (levels: 10) and valence (gains vs. omitted rewards) (levels: 2). Since it was not known whether reward value contributes linearly to the scalp field map, we tested different, monotonic functions to relate reward with the electrophysiological data with the goal of maximizing the correspondence of the actual reward value and the electrophysiological index of reward representation. Reward values x_i were therefore transformed using a power function with parameter α (α < 1: concave function, α = 1: linear function, α > 1: convex function).

$$x_i' = x_i^{\alpha}, \qquad 1)$$

where i is the reward level, and x is the reward (ranging from 0 to 1), and x_i' is the covariate used for the computation of the covariance maps. α was varied in the range of 0.01 to 10 with increments of 0.1. For each subject and value of α, covariance maps β between the transformed reward values and the potentials at each electrode and each included point in time were computed as follows:

$$\beta_{t,e} = \sum_{i=1}^{10} v_{i,t,e} * x_i', \qquad 2)$$

where v is the scalp potential at electrode e, time-point t, and reward level i. These covariance maps were then used to compute, for each reward level, an electrophysiological index $\bar{s}_i$ of reward using the following equation (Koenig et al. 2008):

$$s_{t,i} = \sum_{e=1}^{m} v_{i,t,e} * \beta_{t,e}, \qquad 3)$$

and where $\bar{s}_i$ is the mean of $s_{t,i}$ across time.

The correspondence between $\bar{s}_i$ and x_i was defined by the squared Pearson correlation coefficient r^2 between the two vectors, which is equivalent to the percent

of common variance. The individual optimal α was defined at where this correspondence was maximal. In a next step, we assessed whether the r^2 – values and αs' of best fitting functions significantly differ from the corresponding r^2 – values and a linear function ($\alpha = 1$), using Wilcoxon-signed-rank-tests and paired t-tests, where appropriate. The median of the α-values of the best fitting functions entered the randomization test, described in the following section. To visually confirm the goodness of fit of the value functions, the values of $s_{t,i}$ were plotted.

According to Koenig et al. (2008) a randomization procedure (5000 iterations) was used to identify at which time points of the ERP the global scalp field potentials significantly covaried with the beforehand determined best fitting value function. Since this test calculates whether the ERP-topography covaries above chance level for each time-frame independently, the problem of multiple testing needs to be addressed. Following the same rationale of randomization statistics as for determining significance levels for each time-frame, we calculated whether the duration of a time-window of continuous significant covariation might be observed by chance. Thus, the probability of a falsely detecting certain duration of a significant effect was computed. Details on this particular test are explicated by Koenig and Melie-Garcia (2009, 2010). Results are reported with a threshold for significance of $p < 0.01$. For significant *($p<0.01$)* time-windows the false positive probability of the duration (FPP-D) is indicated. The whole analytical procedure was conducted for the won outcome conditions and the reward omission outcome conditions separately. Since the variable reward valence has only two levels and can be considered as a special case of a covariational analysis (with parameters of 1 for won and -1 for omission) (Koenig et al., 2008) the analysis steps of fitting the best function were unnecessary.

Source localization

Because the generated TANCOVA maps represent a linear transformation of the topographical data, they can directly be submitted to source localization procedures (Koenig et al., 2008). The inverse solution of the ERP-data was calculated using standardized low-resolution electromagnetic tomography (sLORETA) (http://www.uzh.ch/keyinst/loreta.htm) (Pascual-Marqui, 2002). This method

computes the current density magnitude (A/mm^2) of each voxel, localizing the neural generators of the electrical activity by assuming similar activation among neighboring neuronal clusters. The solution space was computed on a spherical head model with anatomical constraints (SMAC model, Spinelli et al., 2000) and comprised 3005 solution points equidistantly distributed within the gray matter of the cerebral cortex and limbic structures of the Montreal Neurological Institute (MNI) 152 average brain. Anatomical labels are reported using an appropriate correction from Talairach-Tournoux to MNI space (Brett et al., 2002). The obtained tomography represents the intracerebral generators of the scalp field data accounting for the effects observed in the external variable with the full spatial resolution of the measured data. The graphical rendering of intracerebral sources and the ERP-topographies was performed using the Cartool software (brainmapping.unige.ch/cartool) (Brunet et al., 2011).

5.4.4 Results

Behavioral results

The behavioral task consisted of pseudo-randomly assigned gained and omitted rewards and the subjects were informed that the chance to win was 50 % throughout the experiment. Nevertheless we were interested how frequently subjects changed their choice of color to bet on, depending on the outcome and type of the previous trial. Results indicated no significant difference in the frequency of changing the choice for a color, neither depending on the value at stake ($F_{(9,135)}= 0.942$; $p < 0.491$), nor on the outcomes (gain / loss) ($F_{(1,15)}= 0.262$; $p < 0.616$), nor on the interaction of both ($F_{(9,135)}= 0.492$; $p < 0.878$).

Consistent topography across subjects

The test for consistent ERP topographies of the grand means across subjects revealed significant (p<0.01) consistency for a time-window from -100 ms to 564 ms (with the outcome as temporal reference), with an inconsistent time-window at 132-140 ms. It is noteworthy that such a short period of inconsistency within a larger time-window of consistent ERP topography typically occurs when ERP topographies change polarity, indicating that ERP sources are in transition to new stable states. The topography of the grand mean of gain-trials was consistent across subjects from -72 ms to 544 ms. Similarly, the grand mean ERP topography of all omission trials was consistent from -112 ms to 568 ms, with inconsistent time-frames at 132 ms - 140 ms, 396 ms - 408 ms and 464 ms - 524 ms. The information of the obtained consistent time-frames was submitted to the proceeding analysis steps of reward value function estimation and the TANCOVA (Fig 3a).

Estimation of Value Functions

The value functions for gains and omissions were estimated subject-wise according to the criterion of the maximal sum of explained variance in the ERP-data during the time of consistent topography. For both, gains and omissions convex functions fitted the ERP-data best (α_{gains}*: Mdn = 2.41, median absolute deviation (MAD) = 4.28;* $\alpha_{omission}$*: Mdn= 3.56, MAD =3.21)* (see Fig. 2). Wilcoxon-signed-rank-tests indicated that $\alpha_{omission}$ differed significantly *(Z=2.694, p<0.007)* from α = 1 (linear function) and that there is a trend for a significant difference between α_{gains} *(Z=1.890, p<0.059)* and α =1. Furthermore, paired t-tests revealed that the functions with optimized αs' explain significantly more variance in the ERPs than linear functions *(gains: $T_{(15)}$=3.991; p<0.001; omission: : $T_{(15)}$=4.238; p<0.001*.)

The model functions with optimized α's explained on average 49.66% of variance in the omission ERPs during the time of consistent topography. For gains the functions with optimized α's explained on average 49.86% of variance in the gain ERPs during the time of consistent topography.

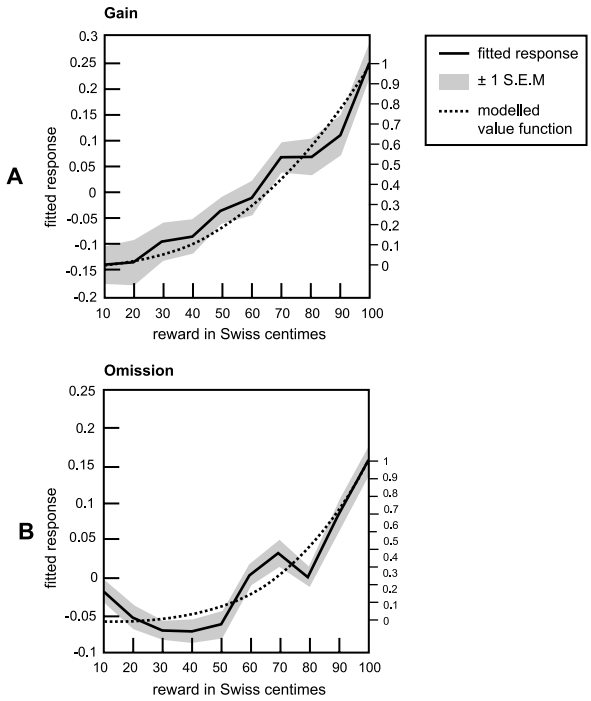

Figure 2. *Electroencephalographically derived value functions*. Mean electrophysiological indices of reward ($\bar{s}_i$, see equation 3 for details) as function of actual reward for the gain and omission conditions. Solid lines show the average across consistent time-frames and subjects and indicate a convex, non-linear relations between monetary rewards and ERP-responses. (Grey areas represent ± 1 standard error of the mean). The dotted lines illustrate the estimated value functions, which corresponded most closely to the exhibited ERP-responses and thus explained most variance in the data.

Topographic Analysis of Covariance (TANCOVA)

The TANCOVA on the variable valence revealed significantly ($p < 0.01$) covarying EEG topographies in the time-windows 268-304 ms *(FPP-D ≤ 0.036)* and 464-508 ms *(FPP-D ≤ 0.028)* post outcome onset. Unexpectedly early (16ms after onset of outcomes to 40ms) there was a trend ($p<0.05$) for significantly differing ERP-topographies with respect to valence. The p-value plot indicates that the p-value starts to decrease before the outcome of the game is presented, thus this effect cannot be the result of a physiological reaction to the valence of outcomes. The analysis further

indicated significant ($p < 0.01$) covariance for the variable reward value of won outcomes during the time period of 280ms – 296ms *(FPP-D ≤ 0.056)* and 484ms – 504ms *(FPP-D ≤ 0.038)* post outcome onset. For reward values of omitted outcomes ERP-topographies indicated a trend ($p < 0.05$) for significant covariation with reward value during a time-window of 360ms – 380ms post outcome onset (Fig. 3b). Plots of the electrophysiological index of reward $s_{t,i}$ as function of time and reward level (Fig. 3c) should provide an insight on how the different reward levels contribute to the overall representation of reward across time.

Source localization

sLORETA was used to localize the intracranial generators of the ERP-covariance maps for each time point in the ERPs. The reported intracranial generators represent the averaged time-windows of significant covariance derived in the TANCOVA. Therefore, this approach revealed the relative contribution of intracranial sources covarying with the external variables. Overall, source localization revealed a neuronal network, which sensitively responds to information about rewarding (or disappointing in the case of omissions) outcomes that includes the ventromedial prefrontal cortex (VMPFC), anterior and posterior cingulate cortex (ACC/PCC), the hippocampus and amygdala (Hipp/Amy) and the medial frontal gyrus (MFG).

The point of maximal current source density (CSD) for valence during the time-window 248ms to 312ms was found in VMPFC (MNI: x = -9, y = 42, z= -16). The time-window from 456ms to 520ms indicated maximal CSD in the right Hippocampus / Amygdala (MNI: x= 29, y = -12 z = -26). The covariance maps of value coding after gains at the time-windows of 268ms – 304ms revealed maximal CSD at the left MFG (MNI: x= -32, y= 8, z=60). For the time-window of 480ms – 512ms highest CSD was found at the VMPFC (MNI: x=-3, y=35, z=-21). The covariance maps of value coding after omitted rewards at the time-window of 360ms – 380ms revealed maximal CSD at the right Hippocampus / Amygdala (MNI: x=29, y=-12, z=-26). (Fig. 3e).

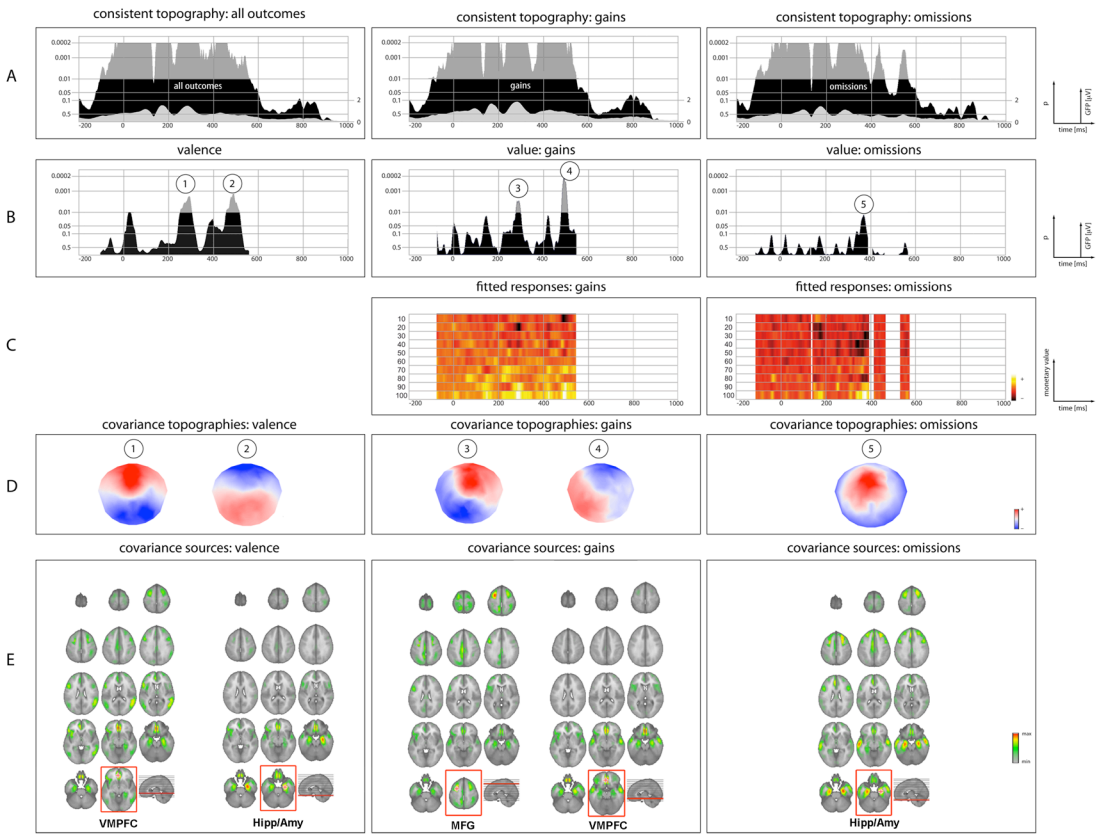

Figure 3. *Overview of ERP- Results*. (a) Results of the topographic consistency test for all outcomes (first row), gains only (second row) and omissions (third row). Black areas indicate the significance level (inversely log-transformed) of the test. Areas exceeding the p<0.01 - mark restrict the time-window of the TANCOVA. The grey areas depicted within indicate the global-field power (GFP). b) Moment-by-moment significance level of the TANCOVA. The height of the area indicates the significance level (inversely log-transformed) of covariation between ERP-topographies and valence (first row), value of gains (second row) and value of omissions (third row). c) Plot of the electrophysiological index of reward $s_{t,i}$ as function of time and reward level (see formula 3). d) Covariance maps of the ERP-data of the respective time-frames of strong covariance. e) Source estimation of the covariance maps. The loci of maximal CSD (e.g. representing the maximal contribution to the covariance in the ERP-topography) are framed in red color. It is worth emphasizing that in all conditions similar sources differently contribute to the covariance at the level of the ERP-topography.

5.4.5 Discussion

This study aimed to extend knowledge on reward processing by investigating ERP-responses at the level of the EEG-topography. This approach offers several attractions: it combines the full spatial representation of EEG-data with a high time resolution and direct access to neuronal signaling. In addition, it is possible to collect a large number of trials within a short time. These factors made it possible to provide novel contributions to the understanding of "how", "where" and "when" reward is processed.

„How" is monetary reward translated into brain activity?

We determined the form of relation between ERP-topographies and associated monetary reward values. This functional form describes how the global response of brain activity is related to stimuli indicating gain and omission of different monetary rewards. Since we assured that these stimuli solely differed with respect to the magnitude of the outcome, it is conceivable that the response of brain activity (measured at the ERP-topography) corresponds to the experienced utility or regret of a more or less favorable outcome. Contrary to our expectations, the results revealed convex value functions for gains and omissions. Therefore, the sensitivity of the electrophysiological response nonlinearly increased for larger values. This finding is in contrast to concave utility functions derived from revealed choices (decision utility) and stimulus-intensity coding functions, following the psychophysics of diminishing sensitivity (Kahneman and Tversky, 1979). It is possible that the discrepancy between the value functions is due to the low monetary values at stake in our experiment. However, as reported for value functions of decision utility, it is assumable that value functions for experienced utility might not change with rising stakes (Fehr-Duda et al., 2010). In addition, it has been shown that reward value is neuronally coded in relation to possible outcomes and not at an absolute scale (Nieuwenhuis et al., 2005; Tobler et al., 2005; Elliott et al., 2008; De Martino et al., 2009; Fujiwara et al., 2009). New experiments are called for to examine the robustness of this unforeseen result;

this allowing to propose conscientious psychological interpretations of value functions for experienced utility and experienced regret.

"Where" is value and valence processed?

Source solutions revealed a network of brain areas, which sensitively responded to information about rewarding (or disappointing) outcomes that includes the VMPFC, ACC/PCC, hippocampus/amygdala and MFG. Interestingly, the characteristic topographies of covariance of the specific time-windows and conditions seems not to result from structurally dissociable neuronal processes as previously suggested (Yacubian et al., 2006, Yeung and Sanfey, 2004). Instead, it seems that a common network is involved in the processing of distinct aspects of reward information; the components are differentially engaged depending on the specific step in processing.

For example, the VMPFC responds sensitively to the valence of the outcome and the value of gains but to a lesser extent to the value of omissions. This is in line with previous studies, showing that activity in the VMPFC increases after rewarding outcomes compared to omissions (Knutson et al., 2003) and is correlated with experienced value (Smith et al., 2010) and pleasantness ratings (Lebreton et al., 2009). In addition, the MFG predominantly responded to information about value but scarcely to valence. This conforms to linear increasing activity with the reward value of gains (Elliott et al., 2003). The source solution indicated most prominent (but not exclusive) omission-sensitive activity in the hippocampus in vicinity to the amygdala. The potential involvement of the amygdala replicates previous results showing that the amygdala encodes negative prediction errors (e.g. worse than expected outcomes) (Yacubian et al., 2006), but also responds to rewards (Breiter et. al., 2001) and is generally believed to encode the emotional significance of stimuli, be it appetitive or aversive (Shabel and Janak, 2009). Similarly – besides the processing of mnemonic functions – the observation of reward dependent variation of activity in the hippocampus is compatible with the key role played by this structure in reward and emotion (Blood and Zatorre, 2001).

We are aware that the precision of the EEG-source localization is limited and it likely cannot distinguish activity, for example, in the amygdala from hippocampal activity. Nevertheless, at a more general level it has been shown that medial-temporal activity or activity in the VMPFC (or orbitofrontal cortex) can be reliably retrieved from scalp EEG using similar source reconstruction techniques as in our study (Lantz et al., 1997, 2001; Zumsteg et al., 2005; Pizzagalli et al., 2003).

"When" is reward information processed?

The results indicate that at a first stage (~250 - 300 ms post-outcome) two factors of outcomes are processed; a coarse evaluation along a good - bad dimension (valence) and a concurrent, finer grained evaluation of positive outcomes (value). The value of omitted rewards covaried with the ERP-topography at a greater latency (~360 ms post-outcome). Importantly, during this time-window ERP-topographies did not differ with respect to the valence of outcomes. The results therefore revealed a concurrent processing of valence and value of gained rewards and a later processing of omitted reward values.

We conjecture that this scheme of brain responses may be driven through cortical input of midbrain reward prediction error (RPE) signals. Seminal experiments of Wolfram Schultz and colleagues have shown that for rewards at chance a positive RPE is generated, which is represented by a phasic increase in spiking activity (Schultz et al., 1997). This increase is scaled to the value of gained rewards (Fiorillo et al., 2003; Bayer and Glimcher, 2005). It was demonstrated that these phasic fluctuations of dopaminergic midbrain activity modulate activity in the ACC (Holroyd and Coles, 2002; Holroyd et al., 2003). Furthermore, in line with our results, several studies revealed that the dopaminergic midbrain is effectively connected (besides others) with the VMPFC, MFG and hippocampus/amygdala (for a review, see Camara et al., 2009). In the case of the omission of a reward, a depression in spiking activity typically follows (Schultz et al., 1997). Therefore, the difference between the depression and any scaled increase of spikes makes it possible that valence and value of gains are concurrently encoded.

For scaled negative RPEs' (e.g. modulated through omitted rewards of different magnitude) the quantification of spike depression appears to be limited (Fiorillo et al., 2003), because the range of the spiking rate of dopaminergic midbrain neurons from the baseline rate (3–8 spikes per second) (Niv and Schoenbaum, 2008) to zero spiking is marginal. This might explain why the value of omitted rewards is not processed at the same time as value of gains in the present study.

However, it has been suggested that scaled negative RPEs' are coded by means of the duration of the pauses in spiking (Bayer et al., 2007). Consequently, it only makes sense to pass the information about the value of negative RPEs from midbrain structures to higher cognitive processing after the full expiration of the pause. In line with this, omitted reward values in this study significantly covaried with the ERP-topography ~110 ms after the first significant effect of valence coding.

Although we were exploring measures at the level of the ERP-topography, by and large our results are supported through findings of research focusing on ERP responses of individual electrodes (Hajcak et al., 2005; Potts et al., 2006; Hewig et al., 2008; Holroyd et al., 2008; San Martin et al., 2010). For example, underpinning the hypothesis of a dopaminergically driven ERP-topographies, Cohen et al., (2007) showed that during a time-window in the range of the first processing of valence and value of gains, power and phase coherence values of ERPs following wins but not losses were modulated by reward probability, which - like reward value - modulates the magnitude of RPEs. Regarding the omission-sensitive ERP-topography, previous studies reported, that the amplitude of the (highly similar in terms of topography and latency) P300 reflects a pure coding of value irrespective of valence in the P300 component (Yeung and Sanfey, 2004; Sato et al., 2005), whereas others indicated that the P300 is sensitive to valence and value (Hajcak et al., 2005; Holroyd and Krigolson, 2007; Wu and Zhou, 2009).

Besides the above-discussed results, which are within the temporal range of previously reported feedback related ERPs, the ERP-topography in a later time-window (~ 470 ms post feedback) significantly varied due to valence and value differences of the gains. Again the ERP-topography did not reflect an influence of the value of omitted rewards. The processing of valence and value of gains similarly involved the VMPFC and Hippocampus/Amygdala. Activity in the VMPFC more strongly covaried with the value of gains, whereas activity in the Hipp/Amy exhibited the strongest source of valence-dependent variation. The finding of a later, yet not

reported reward sensitive ERP-topography demonstrates one of the key advantages of our analysis approach, namely the a-priori unrestrained analysis of all electrodes and time-points of the post-outcome epoch.

To conclude, the present results demonstrate a measure of experienced utility by means of brain activity. In addition, ERP-responses to different aspects of reward information recruit similar but differently weighted neuronal structures in a specific temporal sequence. The time-course of processing argues in favor of dopaminergically-driven activity.

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6 General Discussion

The purpose of **Experiment 1** was to identify the neuronal structures responding to the degree of preference for one out of three desired brands. A further aim of this study was to examine whether the modulation of neural activity by the intensity of brand attractiveness was evident in distinct neural networks during the anticipation of the desired objects and during the evaluation of the receipt of these objects.

To reach these goals, the study used a wheel-of-fortune game comprising an anticipation phase and a subsequent outcome evaluation phase. Inside a 3 Tesla MRI scanner, participants played for chocolate bars of three different brands that differed in subjective attractiveness.

The results of this experiment suggest a graded effect of differently preferred brands onto the incentive value of objectively equivalent rewards. Contrary to the winner-take-all hypothesis (Deppe et al., 2005), neural activity is linearly associated with the subjective brand preference hierarchy. This is in line with studies using objectively varied amounts of money as rewards. Furthermore, the study identifies distinct brand-preference-modulated areas to be active during anticipation and outcome phases.

During the anticipation phase, hemodynamic responses in the left premotor cortex and anterior insula increase in correspondence to brand preferences. These regions of the brain have been associated with motor preparedness (Deiber et al., 1996) and somatic and emotional arousal (Critchley et al., 2000). The activation of a cluster in the (dopaminergic) midbrain possibly affects this increase in arousal, sensorimotor readiness and increased attention (Berridge, 2007).

In the ensuing outcome phase, while participants evaluate the positive game outcome, a distinct neural network commonly associated with attentional processes, sympathetic arousal, and cognitive-emotional evaluation of rewards exhibits preference-modulated activity. In particular, the ventral pallidum (VP) shows preference-sensitive activation. This is in line with previous studys that describe the VP as a central relay station for the distributed brain circuit of core liking (Knutson et

al., 2001b; Tindell et al., 2006), as well as a potential relay station to cortical systems of conscious pleasure.

Contrary to our expectations, we did not find preference-related activity in the ventral striatum (VS), the medial orbitofrontal cortex (MOFC) and the ventromedial prefrontal cortex (VMPFC). This may be due to several reasons. First, fMRI signals in the VS and the OFC are prone to susceptibility artefacts. Because these inferior structures lie close to cavities filled with air, the surrounding magnetic field yields inhomogeinities resulting in signal loss. It is therefore conceivable that fMRI did not reliably capture activity in these regions. Secondly, with regards to the experimental paradigm, to win meant to receive a delayed reward, which was only symbolic at the very moment. Gregorios-Pippas et al., (2009) show that activity in the VS is reduced, when subjects face rewards in the future compared to instant rewards. As a third reason, the properties of the reward scheme might explain the lack of activation in prominent reward-structures like the VS, MOFC and VMPFC: Participants could lose a once gained reward in any subsequent trial. Therefore, the expected reward value and consequently VS activity decreases because for a specific gained reward the probability to keep it over the whole experiment is small. Supporting this notion, a recent fMRI study demonstrates that neural activity in the ventral striatum correlates with the expected probability for a reward and therefore decreases for small probabilities (Abler et al., 2006).

In summary, the study suggest that neural activation in reward processing structures is modulated by stimuli varying in subjective reward intensity. Furthermore, we show that fMRI makes it possible to depict even small differences in preference. As a consequence, the question arises whether fMRI may be directly applicable in marketing research. The greatest factor arguing against widely applied fMRI based screenings is obviously the cost, which reflects a multiple compared to classical market-research screenings. Furthermore, fMRI is limited to a restricted group of subjects that have no metallic implants, cardiac pacemakers, and are not pregnant. In addition, fMRI is very noisy and aggravating for subjects, challenging valid measures of, for example, emotional responses to products. We suggest an alternative approach that uses fMRI to cross-validate market-research instruments. This validation approach is not part of this thesis, but a comprehensive introduction is given by Lutz Jäncke & Raimund Wildner, (2010)

The primary goal of the follow-up **Experiment 2** was to replicate and strengthen the findings of the Experiment 1.Another key question was, whether the observed effects of brand preference on neuronal activity would generalize across different reward categories.

Due to the lack of finding of VS, OFC and VMPFC activity in Experiment 1, we decided to adapt the experimental paradigm with respect to the reward scheme. This time, participants could increase reward probabilities rather than gain (as well as lose) rewards. Again, a wheel-of-fortune game comprising an anticipation phase and a subsequent outcome phase was implemented. Participants played for vouchers for sneakers of three different brands that differed in subjective attractiveness.

We also tried to circumvent the problem of singal loss in inferior structures by modifiying the fMRI scanning sequence. To improve signal-to-noise ratios in these areas, the field-of-view was tilted with an angle of 30° with respect to the AC-PC line (Deichmann et al., 2003).

Overall, the analysis inferred similar structures, suggesting reliable activation of reward related-brain structures to differentially valued rewards. In line with Experiment 1, the data indicate that playing for more preferred rewards compared to less preferred rewards induces increased neural activation in structures commonly linked to reward processing. Results furthermore suggest the proposed distinction between anticipatory and evaluative aspects of reward processing (Knutson et al., 2001b). Thus, the observed effects seem to generalize across different reward categories. In addition, the study shows that increasing the subjects' chance of obtaining a reward elicits neural activity comparable to winning primary reinforcers or accumulating monetary rewards.

In contrast to Experiment 1, activity in the VS and the MPFC correlates with the individual preferences for the sneaker brands. This difference in activity patterns between the experiments demonstrates that only minor changes the experimental design may greatly influence results of fMRI experiments. This highlights the necessity to use fMRI as a hypothesis driven method instead of post ex facto "brain reading".

The **second part of Experiment 2** investigates the characteristics of the hemodynamic response patterns in the VS, using a different analysis approach. Several earlier studies show that dopaminergic midbrain neurons of monkeys and fMRI activity in the human VS encode largely similar aspects of rewards. We

therefore aimed to test whether dopaminergic midbrain firing patterns reported in a recent sinlge cell primate study of Tobler et al. (2005) could predict the characteristic fMRI responses of the VS. Secondly, we sought to investigate whether the effect of reward value "gain-adaptation" in dopamine neurons, reported in same study, is also evident at the level of the VS in humans.

Results indicate that hemodynamic responses in the VS largely follow the predictions of dopaminergic midbrain responses in monkeys. In agreement with Tobler et al.'s (2005) findings, activity in the VS increases as a function of reward magnitude during the expectation of future rewards. Furthermore, fMRI activity increases after gaining rewards, though independently of reward magnitude. This reward magnitude insensitive response is in line with the reported effect of reward prediction error "gain-adaptation" (Tobler et al., 2005). Taking the congruencies between activity in the dopaminergic midbrain and VS into account, it seems reasonable to hypothesize that midbrain dopamine activity largely influences activity in the VS and vice versa. However, hemodynamic responses in the VS after the omission of rewards do reflect the magnitude of the missed rewards. This finding contradicts the observed magnitude-*indifferent* (due to "gain-adaptation") dopaminergic midbrain activity in response to reward omission in non-human primates. Therefore, the partly rejection of the hypothesis of dopaminergic midbrain – VS interaction induces, that after the omission of rewards, the VS receives different than the dopaminergic midbrain input. We explored possible modulatory sources of the graded negative response in the VS using a psychophysiological interaction analysis (PPI). The PPI reveales that a cluster in the brainstem, in vicinity of the dorsal raphe nucleus (dRN), a cluster in the lateral OFC and the ACC changes their effective connectivity to the VS. Single cell recording studies of non-human primates show, that the dRN inhibits dopaminergic function in many terminal fields such as the striatum (Kapur and Remington, 1996). Daw et al., (2002) suggests that serotonin may act as an opponent to dopamine. It is therefore conceivable that the serotonergic dRN down-regulates dopamine release in the VS. Also, the OFC is predestined to influence activity in the VS. The lateral OFC is widely interconnected to sensory structures within the brain (Padoa-Schioppa and Assad, 2006) and is active during the evaluation of punishing stimuli (Kringelbach, 2005). Furthermore, the VS receives major projections from the lateral OFC (Haber et al., 1995). It is consequently likely that the lateral OFC evaluates sensory information about a punishing event which subsequently down-regulates activity in the VS. The

ACC is possible not down-regulating activity in the VS, but is itself up regulated through decreased activity in the VS. The ACC receives strong inhibitory input from dopaminergic structures, which supports the stated interpretation. Consequently, when the outcome of an event is worse than expected, pyramidal cells in the ACC are disinhibited, resulting in the well explored event-related potential (ERP), termed the error related negativity (ERN) or feedback error related negativity (FRN) in electroencephalograms (EEG) (Holroyd and Coles, 2002). Thus, a highly preferred reward that is not obtained represents a more relevant violation of expectancy than the omission of a less preferred reward. Neurons in the ACC may process this violation and trigger the subsequent (re)formation of future expectations.

A third study further investigates the evaluation of rewarding outcomes, using the method of EEG. EEG tracks electrophysiological changes elicited through brain activity in a range of milliseconds. With state-of-the-art high-density electrode arrays it is possible to localize intracortical generators with a precision of a few cubic centimetres. However, common practice of EEG analyses often only examine single electrodes within a predefined time-window of interest, which renders a poor (univariate) representation of multivariate data. The aim of **Experiment 3** was to determine at which time-windows after feedback about rewards ERP topographies covary significantly with reward values of gained and omitted rewards. Taking this approach, we use the full spatial and temporal properties of the EEG data. In addition, we propose a new method to indicate the nature of relationship between the EEG signals and reward magnitudes, therefore providing a psychophysiology-based value function for money.

In Experiment 3 subjects gambled for different amounts of money ranging from 10 Swiss centimes to 1 Swiss franc in decrements of 10 centimes.

Results indicate that the feedback about the outcome of the gambles is first evaluated with respect to the valence (gain vs. omission) within a time range of the feedback related negativity (FRN). Within this time-window (250 – 300ms post outcome) ERP topographies vary also in relation to the value of gains, suggesting a finer grained evaluation. The cerebral sources accounting for the effects on the scalp topography are localized within the medial prefrontal cortex (MPFC). The evaluation of the value of omitted rewards is observable 370ms post outcome and yields an overlapping but slightly more frontal intracerebral source.

This asymmetric processing of gained and omitted reward values can be explained in view of the dopamine reward prediction error theory. According to Schultz et al., (1997) for rewards at chance a positive prediction error is generated, which is represented by a phasic increase in spiking activity in dopamine neurons. This increase scales to the reward value (Bayer et al., 2007) and might therefore account for the covariation of EEG topographies and gained reward values. In contrast, the study of Bayer et al., (2007) reveales that negative reward prediction errors scale to the value of missed rewards with respect to the duration of the pause in spiking. This explains the later covarying ERP-topography for omitted reward values, since the information about the value of the omitted reward is only available after the expiration of the pause.

Using a novel analysis approach, we additionally infer from the experimental data in what relation reward value and EEG maps covary. We observe for gains as well as omitted rewards convex functions. This indicates that the sensitivity of the EEG response disproportionally increases for larger values. This finding is in contrast to behaviourally derived value functions, commonly exhibiting the psychophysics of diminishing sensitivity. We believe that the low range of monetary values at stake causes this discrepancy. Therefore the results cannot be generalized to monetary value functions of greater values. However, using a modified reward scheme should render such a generalization.

The findings of later, yet not reported, reward sensitive EEG topographies demonstrate one of the key advantages of the presented analysis approach: It offers the possibility of a-priori unrestrained analyses of all electrodes and time-points.

Regarding the results of the conducted experiments and other studies as a whole, it appears that the dopamine system is always involved as a root. This system handles the processing of a vast variety of rewards using simple computational rules. It is fascinating that essentially the same neuronal mechanisms as found, for instance, in the brain of a rat also enable humans to make decisions in a complex world. For example, the decision-making involved in the stock market investments likely employs the same basic mechanisms as the ones needed by a neanderthaler thousands of years ago, walking through the forest and deciding to pick berries or hunt animals. Neuronal structures like the VS, VMPFC, and midbrain dopamine areas may be regarded as “reward-gauges”. Correlating neuronal activity in these areas with behavioural measures offers the opportunity to obtain objective measures of incentive

and hedonic valuation. Consequently, modern neuroimaging techniques provide insight in motivational behaviour, decision-making but also addictive behaviour at an introspective-independent level.

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8 Curriculum Vitae

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Swiss citizen, married, born 14.12.1979

EDUCATION

2007 – 2010	**Ph.D. degree at the University of Zurich (summa cum laude)** Department of Psychology, Laboratory of Neuropsychology (Supervisor Prof. Dr. rer. nat. Lutz Jäncke) Research Project: Neural representations of subjective value
2001 – 5/2007	**Lic. Phil. degree at University of Zurich** Department of Psychology Major: psychology, neuropsychology Minor: neuroinformatics, psychopatholgy
1997 – 1998	**Student exchange year, Maroondha Secondary School, Croydon, VIC, Australia**

WORKING EXPERIENCE / INTERNSHIPS

2010 – now	**Institute of Psychology, Laboratory for Social and Affective Neuroscience, University Basel, Switzerland** Post-Doctoral Assistant Research in the field of social and non-social decision-making and learning, using neuroimaging, pharmacological, behavioural and genetics methods. (Prof. Daria Knoch)
2007 – 2010	**Institute of Psychology, Laboratory of Neuropsychology, University Zurich** Scientific Assistant Research in the field of the neuronal representation and processing of value, using EEG and fMRI. (Prof. Lutz Jäncke)
1/2006 – 5/2007	**Institute of Psychology, Laboratory of Neuropsychology, University Zurich** Tutorial Assistant

Programming of software tools for data analysis and implementation of experimental protocols.

11/2004 – 3/2005 **Allgemeines Krankenhaus Wien, Psychiatry, Vienna**
Clinical Internship.
Supervision and diagnosis of patients with acute psychiatric disorders at the intensive care unit of the psychiatric division.
(Prof. Dr. Richard Frey)

2000 – 2001 **Becker AV, Zurich**
Internship
Job Profile: Video editor and production assistant

1997 – 2006 **Institute of Virtual Production, ETH Zurich**
Tutorial Assistant
Preparation of presentations and design / maintenance of the website of the institute.
(Prof. J. Reissner)

In between Freelance work in graphics-design and web-design, using Flash Action Script, Javascript, CSS, HTML and PHP.

Storyboard, design-concept and animation of a tutorial cartoon about "Do's and Don'ts" of video conferencing: http://www.anamorph.ch/flash-design-video-conferencing-01.html

Programming and design of websites:
www.bodegabar.ch
www.tobiasheinemann.ch

COMPETENCES

- Standard Electroencephalography (EEG), functional and structural magnetic resonance imaging (fMRI/sMRI) and behavioural statistical data analysis procedures
- Data reduction using clustering methods (Microstates clustering, independent component analysis)
- Non-parametric randomization statistics
- Neuronal connectivity models in fMRI and EEG
- Intracortical inverse solutions for EEG
- Computational modelling of behaviour
- Development of custom-tailored analysis procedures in MATLAB
- Development and implementation of multiplayer, interactive, large scale experimental paradigms
- Maintenance of EEG-system
- MATLAB, R, SPSS, SPM, FSL, Brainvision Analyzer, Cartool, sLORETA, Presentation, E-Prime, ZTree
- Fluent written and spoken German and English, basic proficiency in French
- Teaching: Seminar: "Bildgebende Verfahren: Auswertung von fMRI-Studien" at the University of Zurich

- Supervision of master theses and Ph.D. students

RESEARCH PROJECTS

- Neuronal representation of expected and experienced value
- Pharmaco-genetic modulation of social and non-social decision making
- Interrelation between genotype, resting-state EEG and decision making
- EEG topography features as predictors for risk taking
- Learning about trustworthiness
- Interaction between intrinsic and extrinsic motivation

PEER-REVIEWED PUBLICATIONS

Pedroni, A., Langer, N., Koenig, T., Allemand, M., and Jäncke, L. (2011). Electroencephalographic topography measures of experienced utility. *J Neurosci* 31, 10474-10480.

Pedroni, A., Koeneke, S., Velickaite, A., and Jäncke, L. (2011). Differential magnitude coding of gains and omitted rewards in the ventral striatum. *Brain Res* 1411, 76-86.

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Cheetham, M., **Pedroni, A.,** Antley, A., Slater, M., and Jäncke, L. (2009). Virtual milgram: empathic concern or personal distress? Evidence from functional MRI and dispositional measures. *Front Hum Neurosci* 3, 29.

Koeneke, S.*, **Pedroni, A.*,** Dieckmann, A., Bosch, V., and Jäncke, L. (2008). Individual preferences modulate incentive values: Evidence from functional MRI. *Behav Brain Funct* 4, 55. (*shared first co-authorship)

Pedroni, M., Bay, T., Oriol, M., and **Pedroni, A.** (2007). Open source projects in programming courses. *ACM SIGCSE Bulletin* 39, 454-458.

Nadig, K, **Pedroni, A.,** Luechinger, R., Jäncke, L., Lutz, K. The rewarding value of good motor performance in the context of monetary incentives (under review)

Langer, N., **Pedroni, A.**, Jäncke, L., The Problem of Thresholding in Small-World Network Analysis (in preparation)

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Eisenegger, C.*, **Pedroni, A.***, Rieskamp, J., Zehnder, C., Fehr, E., Ebstein, R., Knoch, D., Learning How to Differentiate Friend From Foe: The Role of the Dopaminergic System (in preparation) (*shared first co-authorship)

Pedroni, A., Eisenegger C., Hartmann, M., Fischbacher, U., Knoch D. Dopaminergic Modulation of Reward and Punishment in Social Interaction (in preparation)

Pedroni, A., Koeneke, S., Dieckmann, A., Bosch, V., Jäncke, L. (2010) Brand-preference modulated neural activity during expectation and evaluation of a reward. Invited paper presented at the NeuroPsychoEconommics/ CONNECS Copenahagen, Denmark.

Pedroni, A., Langer, N., Koenig, T., Allemand, M., and Jäncke, L. (2011). Electroencephalographic topography measures of experienced utility. Paper to be presented at the Alpine Brain Imaging Meeting, Champéry, Switzerland.

Pedroni, A., Eisenegger, C., Rieskamp, J., Zehnder, C., Fehr, E., Ebstein, R., Knoch D., (2011) Building trust: L-DOPA and DAT polymorphism modulate learning in a repeated trust game. Invited paper presented at the 41st annual conference of the International Society of Psychoneuroendocrinology (ISPNE), Berlin, Germany.

Pedroni, A., Eisenegger, C., Zehnder, C., Fehr, E., Knoch, D. (2011). Dopaminergic modulation of learning about a person's trustworthiness. Paper to be presented at the Swiss Society for Neuroscience Annual Meeting, Basel, Switzerland

Hartmann, M., **Pedroni, A.,** Eisenegger, C., Fischbacher, U., Fehr, E., Knoch, D. (2011) Single administration of levodopa modulates reward sensitivity but not self-control in a social decision making task. Paper to be presented at the Swiss Society for Neuroscience Annual Meeting, Basel, Switzerland

Pedroni, A., Gianotti, L., Knoch, D., (2012) EEG microstate parameter predict decisions in a risk-taking task. Paper to be presented at the Alpine Brain Imaging Meeting, Champéry, Switzerland.